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(54) **Title:** STREPTOCOCCUS PYOGENES ANTIGENS

(57) **Abstract:** The present invention discloses isolated nucleic acid molecules encoding a hyperimmune serum reactive antigen or a fragment thereof as well as hyperimmune serum reactive antigens or fragments thereof from S. pyogenes, methods for isolating such antigens and specific uses therefor

Streptococcus pyogenes Antigens

The present invention relates to isolated nucleic acid molecules, which encode antigens for *Streptococcus pyogenes*, which are suitable for use in preparation of pharmaceutical medicaments for the prevention and treatment of bacterial infections caused by *Streptococcus pyogenes*.

Streptococcus pyogenes, also called group A streptococci (GAS), is an important gram-positive extracellular bacterial pathogen and commonly infects humans. GAS colonize the throat or skin and are responsible for a number of suppurative infections and non-suppurative sequelae. It is primarily a disease of children and causes a variety of infections including bacterial pharyngitis, scarlet fever, impetigo and sepsis in humans. Decades of epidemiological studies have led to the concept of distinct throat and skin strains, where certain serotypes are often associated with throat or skin infections, respectively {Cunningham, M., 2000}. GAS have been discovered responsible for streptococcal toxic shock syndrome associated necrotizing fasciitis which is recently resurgent in the USA {Cone, L. et al., 1987; Stevens, D., 1992} and has been described as the "flesh eating" bacterium which invades skin and soft tissues leading to tissue or limb destruction.

Several post-streptococcal sequelae may occur in humans subsequent to infection, such as acute rheumatic fever, acute glomerulonephritis and reactive arthritis. Acute rheumatic fever and rheumatic heart disease are of these the most serious autoimmune sequelae and have led to disability and death of children worldwide. *S. pyogenes* can also causes severe acute diseases such as scarlet fever and necrotizing fasciitis and has been associated with Tourette's syndrome, tics and movement and attention disorders.

Group A streptococci are the most common bacterial cause of sore throat and pharyngitis and account for at least 16% of all office calls in a general medical practice, season dependent {Hope-Simpson, R., 1981}. It primarily affects children in school-age between 5 to 15 years of age {Cunningham, M., 2000}. All ages are susceptible to spread of the organism under crowded conditions, for example in schools. GAS are not considered normal flora though, but pharyngeal carriage of group A streptococci can occur without clinical symptoms.

Group A streptococci can be distinguished by the Lancefield classification scheme of serologic typing based on their carbohydrate or classified into M protein serotypes based on a surface protein that can be extracted by boiling bacteria with hydrochloric acid. This has led to the identification of more than 80 serotypes, which can also be typed by a molecular approach (emm genes). Certain M protein serotypes of *S. pyogenes* are mainly associated with pharyngitis and rheumatic fever, while others mainly seem to cause pyoderma and acute glomerulonephritis {Cunningham, M., 2000}.
Also implicated in causing pharyngitis and occasionally toxic shock are group C and G streptococci, which must be distinguished after throat culture {Hope-Simpson, R., 1981; Bisno, A. et al., 1987}.
Currently, streptococcal infections can only be treated by antibiotic therapy. However, 25-30% of those treated with antibiotics show recurrent disease and/or shed the organism in mucosal secretions. There is at present no preventive treatment (vaccine) available to avoid streptococcal infections.

Thus, there remains a need for an effective treatment to prevent or ameliorate streptococcal infections. A vaccine could not only prevent infections by streptococci, but more specifically prevent or ameliorate colonization of host tissues, thereby reducing the incidence of pharyngitis and other suppurative infections. Elimination of non-suppurative sequelae such as rheumatic fever, acute glomerulonephritis, sepsis, toxic shock and necrotizing fasciitis would be a direct consequence of reducing the incidence of acute infection and carriage of the organism. Vaccines capable of showing cross-protection against other streptococci would also be useful to prevent or ameliorate infections caused by all other beta-hemolytic streptococcal species, namely groups A, B, C and G.

A vaccine can contain a whole variety of different antigens. Examples of antigens are whole-killed or attenuated organisms, subfractions of these organisms/tissues, proteins, or, in their most simple form, peptides. Antigens can also be recognized by the immune system in form of glycosylated proteins or peptides and may also be or contain polysaccharides or lipids. Short peptides can be used since for example cytotoxic T-cells (CTL) recognize antigens in form of short usually 8-11 amino acids long peptides in conjunction with major histocompatibility complex (MHC). B-cells can recognize linear epitopes as short as 4-5 amino acids, as well as three-dimensional structures (conformational epitopes). In order to obtain sustained, antigen-specific immune responses, adjuvants need to trigger immune cascades that involve all cells of the immune system necessary. Primarily, adjuvants are acting, but are not restricted in their mode of action, on so-called antigen presenting cells (APCs). These cells usually first encounter the antigen(s) followed by presentation of processed or unmodified antigen to immune effector cells. Intermediate cell types may also be involved. Only effector cells with the appropriate specificity are activated in a productive immune response. The adjuvant may also locally retain antigens and co-injected other factors. In addition the adjuvant may act as a chemoattractant for other immune cells or may act locally and/or systemically as a stimulating agent for the immune system.

Approaches to develop a group A streptococcal vaccine have focused mainly on the cell surface M protein of *S. pyogenes* {Bessen, D. et al., 1988; Bronze, M. et al., 1988}. Since more than 80 different M serotypes of *S. pyogenes* exist and new serotypes continually arise {Fischetti, V., 1989}, inoculation with a limited number of serotype-specific M protein or M protein derived peptides will not likely be effective in protecting against all other M serotypes. Furthermore, it has been shown that the M protein contains an amino acid sequence, which is immunologically cross-reactive with human heart tissue, which is thought to account for heart valve damage associated with rheumatic fever {Fenderson, P. et al., 1989}.

There are other proteins under consideration for vaccine development, such as the erythrogenic toxins, streptococcal pyrogenic exotoxin A and streptococcal pyrogenic exotoxin B {Lee, P. K., 1989}. Immunity to these toxins could possibly prevent the deadly symptoms of streptococcal toxic shock, but it may not prevent colonization by group A streptococci.

The use of the above described proteins as antigens for a potential vaccine as well as a number of additional candidates {Ji, Y. et al., 1997; Guzman, C. et al., 1999} resulted mainly from a selection based on easiness of identification or chance of availability. There is a demand to identify efficient and relevant antigens for S. pyogenes.

The present inventors have developed a method for identification, isolation and production of hyperimmune serum reactive antigens from a specific pathogen, especially from *Staphylococcus aureus* and *Staphylococcus epidermidis* (WO 02/059148). However, given the differences in biological property, pathogenic function and genetic background, *Streptococcus pyogenes* is distinctive from *Staphylococcus* strains. Importantly, the selection of sera for the identification of antigens from *S. pyogenes* is different from that applied to the *S. aureus* screens. Three major types of human sera were collected for that purpose. First, healthy adults below <45 years of age preferably with small children in the household were tested for nasopharyngeal carriage of *S. pyogenes*. A large percentage of young children are carriers of *S. pyogenes*, and they are considered a source for exposure for their family members. Based on correlative data, protective (colonization neutralizing) antibodies are likely to be present in exposed individuals (children with high carriage rate in the household) who are not carriers of *S. pyogenes*. To be able to select for relevant serum sources, a series of ELISAs measuring anti-*S. pyogenes* IgG and IgA antibody levels were performed with bacterial lysates and culture supernatant proteins. Sera from high titer non-carriers were included in the genomic based antigen identification. This approach for selection of human sera is basically very different from that used for *S. aureus*, where carriage or noncarriage state cannot be associated with antibody levels.

Second, serum samples from patients with pharyngitis were characterized and selected in the same way. The third group of serum samples obtained from individuals with post-streptococcal sequellae - such as acute rheumatic fever and glomerulonephritis - were used mainly for validation purposes. This latter group helps in the exclusion of epitopes, which induce high levels of antibodies in these patients, since post-streptococcal disease is associated with antibodies induced by GAS and reactive against human tissues, such as heart muscle, or involved in harmful immune complex formation in the kidney glomeruli. The genomes of the two bacterial species *S. pyogenes* and *S. aureus* by itself show a number of important differences. The genome of *S. pyogenes* contains app. 1.85 Mb, while *S. aureus* harbours 2.85 Mb. They have an average GC content of 38.5 and 33%, respectively and approximately 30 to 45% of the encoded genes are not shared between the two pathogens. In addition, the two bacterial species require different growth conditions and media for propagation. While *S. pyogenes* is a strictly human pathogen, *S. aureus* can also be found infecting a range of warm-blooded animals. A list of the most important diseases, which can be inflicted by the two pathogens is presented below. *S. aureus* causes mainly nosocomial, opportunistic infections: impetigo, folliculitis, abscesses, boils, infected lacerations, endocarditis, meningitis, septic arthritis, pneumonia, osteomyelitis, scalded skin syndrome (SSS), toxic shock syndrome. *S. pyogenes* causes mainly community aquired infections: streptococcal sore throat (fever, exudative tonsillitis, pharyngitis), streptococcal skin infections, scarlet fever, puerperal fever, septicemia, erysipelas, perianal cellulitis, mastoiditis, otitis media, pneumonia, peritonitis, wound infections, acute glomerulonephritis, acute rheumatic fever; toxic shock-like syndrome, necrotizing fasciitis.

The problem underlying the present invention was to provide means for the development of medicaments such as vaccines against *S. pyogenes* infection. More particularly, the problem was to provide an efficient, relevant and comprehensive set of nucleic acid molecules or hyperimmune serum reactive antigens from *S. pyogenes* that can be used for the manufacture of said medicaments.

Therefore, the present invention provides an isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence which is selected from the group consisting of:

a) a nucleic acid molecule having at least 70% sequence identity to a nucleic acid molecule selected from **Seq ID No** 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150.
b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b), or c)
e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid molecule defined in a), b), c) or d).

According to a preferred embodiment of the present invention the sequence identity is at least 80%, preferably at least 95%, especially 100%.

Furthermore, the present invention provides an isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence selected from the group consisting of

a) a nucleic acid molecule having at least 96% sequence identity to a nucleic acid molecule selected from **Seq ID No** 64,
b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b) or c),

e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).

According to another aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of

a) a nucleic acid molecule selected from **Seq ID** No 3, 36, 47-48, 55, 62, 72, 80, 84, 95.
b) a nucleic acid molecule which is complementary to the nucleic acid of a),
c) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).

Preferably, the nucleic acid molecule is DNA or RNA.

According to a preferred embodiment of the present invention, the nucleic acid molecule is isolated from a genomic DNA, especially from a S. *pyogenes* genomic DNA.

According to the present invention a vector comprising a nucleic acid molecule according to any of the present invention is provided.

In a preferred embodiment the vector is adapted for recombinant expression of the hyperimmune serum reactive antigens or fragments thereof encoded by the nucleic acid molecule according to the present invention.

The present invention also provides a host cell comprising the vector according to the present invention.

According to another aspect the present invention further provides a hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to the present invention.

In a preferred embodiment the amino acid sequence (polypeptide) is selected from the group consisting of **Seq ID No** 151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244 and 246-300.

In another preferred embodiment the amino acid sequence (polypeptide) is selected from the group consisting of **SEq ID No** 214

In a further preferred embodiment the amino acid sequence (polypeptide) is selected from the group consisting of **Seq ID No** 153, 186, 197-198, 205, 212, 222, 230, 234, 245.

According to a further aspect the present invention provides fragments of hyperimmune serum-reactive antigens selected from the group consisting of peptides comprising amino acid sequences of column "predicted immunogenic aa" and "location of identified immunogenic region" of Table 1; the serum reactive epitopes of Table 2, especially peptides comprising amino acids 4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425 and 1-114 of **Seq ID** No 151; 5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395 and 29-226 of **Seq ID** No 152; 4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254 and 919-929 of **Seq ID No** 153; 5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360 and 145-305 of **Seq ID No** 154; 15-39,

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1-12 of **Seq ID No** 247; 21-38 of **Seq ID No** 248; 2-22 of **Seq ID No** 254; 15-33 of **Seq ID No** 255; 11-32 of **Seq ID No** 256; 11-28 of **Seq ID No** 259; 10-27 of **Seq ID No** 260; 9-26 of **Seq ID No** 261; 4-16 of **Seq ID No** 263; 1-18 of **Seq ID No** 266; 12-29 of **Seq ID No** 273; 6-23 of **Seq ID No** 276; 1-21 of **Seq ID No** 277; 47-64 of **Seq ID No** 279; 28-45 of **Seq ID No** 285; 18-35 of **Seq ID No** 287; 14-31 of **Seq ID No** 291; 7-24 of **Seq**

ID No 292; 8-25 of Seq ID No 299; 1-20 of Seq ID No 300; 18-33 of Seq ID No 151; 62-72 of Seq ID No 151; 118-131 of Seq ID No 152; 195-220 of Seq ID No 154; 215-240 of Seq ID No 154; 255-280 of Seq ID No 154, 72-81 of Seq ID No 155; 174-186 of Seq ID No 156; 317-331 of Seq ID No 157; 35-59 of Seq ID No 158; 54-84 of Seq ID No 158; 79-104 of Seq ID No 158; 33-58 of Seq ID No 159; 81-101 of Seq ID No 159; 136-150 of Seq ID No 159; 173-186 of Seq ID No 159; 231-251 of Seq ID No 159; 22-48 of Seq ID No 161; 24-39 of Seq ID No 162; 475-489 of Seq ID No 163; 38-56 of Seq ID No 164; 583-604 of Seq ID No 164; 202-223 of Seq ID No 165; 222-247 of Seq ID No 165; 242-267 of Seq ID No 165; 262-287 of Seq ID No 165; 282-307 of Seq ID No 165; 302-327 of Seq ID No 165; 25-48 of Seq ID No 166; 204-217 of Seq ID No 167; 259-276 of Seq ID No 168; 121-139 of Seq ID No 169; 260-267 of Seq ID No 169; 215-240 of Seq ID No 169; 115-140 of Seq ID No 170; 182-204 of Seq ID No 172; 144-153 of Seq ID No 173; 205-219 of Seq ID No 173; 196-206 of Seq ID No 174; 240-249 of Seq ID No 174; 272-287 of Seq ID No 174; 199-223 of Seq ID No 174; 218-237 of Seq ID No 174; 226-249 of Seq ID No 175; 287-306 of Seq ID No 175; 430-449 of Seq ID No 176; 361-375 of Seq ID No 177; 241-260 of Seq ID No 178; 483-502 of Seq ID No 181; 379-396 of Seq ID No 182; 31-51 of Seq ID No 184; 1436-1460 of Seq ID No 186; 1455-1474 of Seq ID No 186; 1469-1487 of Seq ID No 186; 215-229 of Seq ID No 187; 534-561 of Seq ID No 187; 59-84 of Seq ID No 187; 79-104 of Seq ID No 187; 618-635 of Seq ID No 188; 191-203 of Seq ID No 189; 386-398 of Seq ID No 190; 65-83 of Seq ID No 191; 90-105 of Seq ID No 192; 112-136 of Seq ID No 192; 290-209 of Seq ID No 193; 33-50 of Seq ID No 194; 76-90 of Seq ID No 195; 70-88 of Seq ID No 196; 418-442 of Seq ID No 197; 574-585 of Seq ID No 197; 87-104 of Seq ID No 198; 124-148 of Seq ID No 198; 141-152 of Seq ID No 198; 241-248 of Seq ID No 199; 183-198 of Seq ID No 200; 40-57 of Seq ID No 201; 202-217 of Seq ID No 202; 50-74 of Seq ID No 203; 69-93 of Seq ID No 203; 88-112 of Seq ID No 203; 107-127 of Seq ID No 203; 74-92 of Seq ID No 205; 207-232 of Seq ID No 206; 227-252 of Seq ID No 206; 247-272 of Seq ID No 206; 47-60 of Seq ID No 207; 297-305 of Seq ID No 207; 312-337 of Seq ID No 207; 667-384 of Seq ID No 208; 279-295 of Seq ID No 210; 179-198 of Seq ID No 211; 27-51 of Seq ID No 213; 46-70 of Seq ID No 213; 65-89 of Seq ID No 213; 84-108 of Seq ID No 213; 112-141 of Seq ID No 213; 248-260 of Seq ID No 215; 59-78 of Seq ID No 216; 154-170 of Seq ID No 218; 57-73 of Seq ID No 219; 297-314 of Seq ID No 220; 142-157 of Seq ID No 221; 428-447 of Seq ID No 222; 573-593 of Seq ID No 222; 523-544 of Seq ID No 223; 46-70 of Seq ID No 223; 65-89 of Seq ID No 223; 84-108 of Seq ID No 223; 122-151 of Seq ID No 223; 123-142 of Seq ID No 224; 903-921 of Seq ID No 225; 119-136 of Seq ID No 226; 142-161 of Seq ID No 227; 258-277 of Seq ID No 228; 272-300 of Seq ID No 228; 295-322 of Seq ID No 228; 311-343 of Seq ID No 229; 278-304 of Seq ID No 229; 131-150 of Seq ID No 230; 195-218 of Seq ID No 230; 53-70 of Seq ID No 231; 184-208 of Seq ID No 232; 222-246 of Seq ID No 232; 241-265 of Seq ID No 232; 260-284 of Seq ID No 232; 279-303 of Seq ID No 232; 317-341 of Seq ID No 232; 678-696 of Seq ID No 233; 88-114 of Seq ID No 235; 464-481 of Seq ID No 235; 153-172 of Seq ID No 236; 137-155, 166-184 of Seq ID No 236; 215-228 of Seq ID No 236; 37-51 of Seq ID No 237; 53-75 of Seq ID No 237; 232-251 of Seq ID No 237; 318-336 of Seq ID No 237; 305-315 of Seq ID No 238; 131-156 of Seq ID No 238; 258-275 of Seq ID No 241; 107-137 of Seq ID No 243; 138-162 of Seq ID No 243; 157-181 of Seq ID No 243; 195-227 of Seq ID No 243; 62-78 of Seq ID No 244; 567-584 of Seq ID No 245.

The present invention also provides a process for producing a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof according to the present invention comprising expressing one or more of the nucleic acid molecules according to the present invention in a suitable expression system.

Moreover, the present invention provides a process for producing a cell, which expresses a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof according to the present invention comprising transforming or transfecting a suitable host cell with the vector according to the present invention.

According to the present invention a pharmaceutical composition, especially a vaccine, comprising a hyperimmune serum-reactive antigen or a fragment thereof as defined in the present invention or a nucleic acid molecule as defined in the present invention is provided.

In a preferred embodiment the pharmaceutical composition further comprises an immunostimulatory substance, preferably selected from the group comprising polycationic polymers, especially polycationic peptides, immunostimulatory deoxynucleotides (ODNs), peptides containing at least two LysLeuLys motifs, especially KLKL5KLK, neuroactive compounds, especially human growth hormone, alumn, Freund's complete or incomplete adjuvants or combinations thereof.

In a more preferred embodiment the immunostimulatory substance is a combination of either a polycationic polymer and immunostimulatory deoxynucleotides or of a peptide containing at least two LysLeuLys motifs and immunostimulatory deoxynucleotides.

In a still more preferred embodiment the polycationic polymer is a polycationic peptide, especially polyarginine.

According to the present invention the use of a nucleic acid molecule according to the present invention or a hyperimmune serum-reactive antigen or fragment thereof according to the present invention for the manufacture of a pharmaceutical preparation, especially for the manufacture of a vaccine against *S. pyogenes* infection, is provided.

Also an antibody, or at least an effective part thereof, which binds at least to a selective part of the hyperimmune serum-reactive antigen or a fragment thereof according to the present invention is provided herewith.

In a preferred embodiment the antibody is a monoclonal antibody.

In another preferred embodiment the effective part of the antibody comprises Fab fragments.

In a further preferred embodiment the antibody is a chimeric antibody.

In a still preferred embodiment the antibody is a humanized antibody.

The present invention also provides a hybridoma cell line, which produces an antibody according to the present invention.

Moreover, the present invention provids a method for producing an antibody according to the present invention, characterized by the following steps:

- initiating an immune response in a non-human animal by administrating an hyperimmune serum-reactive antigen or a fragment thereof, as defined in the invention, to said animal,
- removing an antibody containing body fluid from said animal, and
- producing the antibody by subjecting said antibody containing body fluid to further purification steps.

Accordingly, the present invention also provides a method for producing an antibody according to the present invention, characterized by the following steps:

- initiating an immune response in a non-human animal by administrating an hyperimmune serum-reactive antigen or a fragment thereof, as defined in the present invention, to said animal,
- removing the spleen or spleen cells from said animal,
- producing hybridoma cells of said spleen or spleen cells,
- selecting and cloning hybridoma cells specific for said hyperimmune serum-reactive antigens or a fragment thereof,
- producing the antibody by cultivation of said cloned hybridoma cells and optionally further purification steps.

The antibodies provided or produced according to the above methods may be used for the preparation of a medicament for treating or preventing *S. pyogenes* infections.

According to another aspect the present invention provides an antagonist which binds to a hyperimmune serum-reactive antigen or a fragment thereof according to the present invention.

Such an antagonist capable of binding to a hyperimmune serum-reactive antigen or fragment thereof according to the present invention may be identified by a method comprising the following steps:

a) contacting an isolated or immobilized hyperimmune serum-reactive antigen or a fragment thereof according to the present invention with a candidate antagonist under conditions to permit binding of said candidate antagonist to said hyperimmune serum-reactive antigen or fragment, in the presence of a component capable of providing a detectable signal in response to the binding of the candidate antagonist to said hyperimmune serum reactive antigen or fragment thereof; and
b) detecting the presence or absence of a signal generated in response to the binding of the antagonist to the hyperimmune serum reactive antigen or the fragment thereof.

An antagonist capable of reducing or inhibiting the interaction activity of a hyperimmune serum-reactive antigen or a fragment thereof according to the present invention to its interaction partner may be identified by a method comprising the following steps:

a) providing a hyperimmune serum reactive antigen or a hyperimmune fragment thereof according to the present invention,
b) providing an interaction partner to said hyperimmune serum reactive antigen or a fragment thereof, especially an antibody according to the present invention,
c) allowing interaction of said hyperimmune serum reactive antigen or fragment thereof to said interaction partner to form a interaction complex,
d) providing a candidate antagonist,
e) allowing a competition reaction to occur between the candidate antagonist and the interaction complex ,
f) determining whether the candidate antagonist inhibits or reduces the interaction activities of the hyperimmune serum reactive antigen or the fragment thereof with the interaction partner.

The hyperimmune serum reactive antigens or fragments thereof according to the present invention may be used for the isolation and/or purification and/or identification of an interaction partner of said hyperimmune serum reactive antigen or fragment thereof.

The present invention also provides a process for *in vitro* diagnosing a disease related to expression of a hyperimmune serum-reactive antigen or a fragment thereof according to the present invention comprising determining the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to the present invention or the presence of the hyperimmune serum reactive antigen or fragment thereof according to the present invention.

The present invention also provides a process for *in vitro* diagnosis of a bacterial infection, especially a *S. pyogenes* infection, comprising analyzing for the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to the present invention or the presence of the hyperimmune serum reactive antigen or fragment thereof according to the present invention.

Moreover, the present invention provides the use of a hyperimmune serum reactive antigen or fragment thereof according to the present invention for the generation of a peptide binding to said hyperimmune serum reactive antigen or fragment thereof, wherein the peptide is an anticaline.

The present invention also provides the use of a hyperimmune serum-reactive antigen or fragment

thereof according to the present invention for the manufacture of a functional nucleic acid, wherein the functional nucleic acid is selected from the group comprising aptamers and spiegelmers.

The nucleic acid molecule according to the present invention may also be used for the manufacture of a functional ribonucleic acid, wherein the functional ribonucleic acid is selected from the group comprising ribozymes, antisense nucleic acids and siRNA.

The present invention advantageously provides an efficient, relevant and comprehensive set of isolated nucleic acid molecules and their encoded hyperimmune serum reactive antigens and fragments thereof identified from *S. pyogenes* using an antibody preparation from multiple human plasma pools and surface expression libraries derived from the genome of *S. pyogenes*. Thus, the present invention fulfils a widely felt demand for *S. pyogenes* antigens, vaccines, diagnostics and products useful in procedures for preparing antibodies and for identifying compounds effective against *S. pyogenes* infection.

An effective vaccine should be composed of proteins or polypeptides, which are expressed by all strains and are able to induce high affinity, abundant antibodies against cell surface components of S. *pyogenes*. The antibodies should be IgG1 and/or IgG3 for opsonization, and any IgG subtype and IgA for neutralisation of adherence and toxin action. A chemically defined vaccine must be definitely superior compared to a whole cell vaccine (attenuated or killed), since components of S. *pyogenes*, which cross-react with human tissues or inhibit opsonization {Whitnack, E. et al., 1985} can be eliminated, and the individual proteins inducing protective antibodies and/or a protective immune response can be selected.

The approach, which has been employed for the present invention, is based on the interaction of group A streptococcal proteins or peptides with the antibodies present in human sera. The antibodies produced against *S. pyogenes* by the human immune system and present in human sera are indicative of the *in vivo* expression of the antigenic proteins and their immunogenicity. In addition, the antigenic proteins as identified by the bacterial surface display expression libraries using pools of pre-selected sera, are processed in a second and third round of screening by individual selected or generated sera. Thus the present invention supplies an efficient, relevant, comprehensive set of group A streptococcal antigens as a pharmaceutical composition, especially a vaccine preventing infection by *S. pyogenes*.

In the antigen identification program for identifying a comprehensive set of antigens according to the present invention, at least two different bacterial surface expression libraries are screened with several serum pools or plasma fractions or other pooled antibody containing body fluids (antibody pools). The antibody pools are derived from a serum collection, which has been tested against antigenic compounds of *S. pyogenes*, such as whole cell extracts and culture supernatant proteins. Preferably, 2 distinct serum collections are used: 1. With very stable antibody repertoire: normal adults, clinically healthy people, who are non-carriers and overcame previous encounters or currently carriers of *S. pyogenes* without acute disease and symptoms, 2. With antibodies induced acutely by the presence of the pathogenic organism: patients with acute disease with different manifestations (e.g. *S. pyogenes* pharyngitis, wound infection and bacteraemia). Sera have to react with multiple group A streptococci-specific antigens in order to be considered hyperimmune and therefore relevant in the screening method applied for the present invention. The antibodies produced against streptococci by the human immune system and present in human sera are indicative of the *in vivo* expression of the antigenic proteins and their immunogenicity.

The expression libraries as used in the present invention should allow expression of all potential antigens, e.g. derived from all surface proteins of *S. pyogenes*. Bacterial surface display libraries will be represented by a recombinant library of a bacterial host displaying a (total) set of expressed peptide sequences of group A streptococci on a number of selected outer membrane proteins (LamB, BtuB, FhuA) at the bacterial host membrane {Georgiou, G., 1997; Etz, H. et al., 2001}. One of the advantages of using recombinant expression libraries is that the identified hyperimmune serum-reactive antigens may be instantly produced by expression of the coding sequences of the screened and selected clones expressing

the hyperimmune serum-reactive antigens without further recombinant DNA technology or cloning steps necessary.

The comprehensive set of antigens identified by the described program according to the present invention is analysed further by one or more additional rounds of screening. Therefore individual antibody preparations or antibodies generated against selected peptides which were identified as immunogenic are used. According to a preferred embodiment the individual antibody preparations for the second round of screening are derived from patients who have suffered from an acute infection with group A streptococci, especially from patients who show an antibody titer above a certain minimum level, for example an antibody titer being higher than 80 percentile, preferably higher than 90 percentile, especially higher than 95 percentile of the human (patient or healthy individual) sera tested. Using such high titer individual antibody preparations in the second screening round allows a very selective identification of the hyperimmune serum-reactive antigens and fragments thereof from *S. pyo*genes.

Following the high throughput screening procedure, the selected antigenic proteins, expressed as recombinant proteins or in vitro translated products, in case it can not be expressed in prokaryotic expression systems, or the identified antigenic peptides (produced synthetically) are tested in a second screening by a series of ELISA and Western blotting assays for the assessment of their immunogenicity with a large human serum collection (> 100 uninfected, > 50 patients sera).

It is important that the individual antibody preparations (which may also be the selected serum) allow a selective identification of the hyperimmune serum-reactive antigens from all the promising candidates from the first round. Therefore, preferably at least 10 individual antibody preparations (i.e. antibody preparations (e.g. sera) from at least 10 different individuals having suffered from an infection to the chosen pathogen) should be used in identifying these antigens in the second screening round. Of course, it is possible to use also less than 10 individual preparations, however, selectivity of the step may not be optimal with a low number of individual antibody preparations. On the other hand, if a given hyperimmune serum-reactive antigen (or an antigenic fragment thereof) is recognized by at least 10 individual antibody preparations, preferably at least 30, especially at least 50 individual antibody preparations, identification of the hyperimmune serum-reactive antigen is also selective enough for a proper identification. Hyperimmune serum-reactivity may of course be tested with as many individual preparations as possible (e.g. with more than 100 or even with more than 1,000).

Therefore, the relevant portion of the hyperimmune serum-reactive antibody preparations according to the method of the present invention should preferably be at least 10, more preferred at least 30, especially at least 50 individual antibody preparations. Alternatively (or in combination) hyperimmune serum-reactive antigens may preferably be also identified with at least 20%, preferably at least 30%, especially at least 40% of all individual antibody preparations used in the second screening round.

According to a preferred embodiment of the present invention, the sera from which the individual antibody preparations for the second round of screening are prepared (or which are used as antibody preparations), are selected by their titer against *S. pyogenes* (e.g. against a preparation of this pathogen, such as a lysate, cell wall components and recombinant proteins). Preferably, some are selected with a total IgA titer above 4,000 U, especially above 6,000 U, and/or an IgG titer above 10,000 U, especially above 12,000 U (U = units, calculated from the OD_{405nm} reading at a given dilution) when the whole organism (total lysate or whole cells) is used as antigen in the ELISA.

The antibodies produced against streptococci by the human immune system and present in human sera are indicative of the in vivo expression of the antigenic proteins and their immunogenicity. The recognition of linear epitopes by antibodies can be based on sequences as short as 4-5 amino acids. Of course it does not necessarily mean that these short peptides are capable of inducing the given antibody in vivo. For that reason the defined epitopes, polypeptides and proteins are further to be tested in

animals (mainly in mice) for their capacity to induce antibodies against the selected proteins in vivo.

The preferred antigens are located on the cell surface or secreted, and are therefore accessible extracellularly. Antibodies against cell wall proteins are expected to serve two purposes: to inhibit adhesion and to promote phagocytosis. Antibodies against secreted proteins are beneficial in neutralisation of their function as toxin or virulence component. It is also known that bacteria communicate with each other through secreted proteins. Neutralizing antibodies against these proteins will interrupt growth-promoting cross-talk between or within streptococcal species. Bioinformatic analyses (signal sequences, cell wall localisation signals, transmembrane domains) proved to be very useful in assessing cell surface localisation or secretion. The experimental approach includes the isolation of antibodies with the corresponding epitopes and proteins from human serum, and the generation of immune sera in mice against (poly)peptides selected by the bacterial surface display screens. These sera are then used in a third round of screening as reagents in the following assays: cell surface staining of group A streptococci grown under different conditions (FACS, microscopy), determination of neutralizing capacity (toxin, adherence), and promotion of opsonization and phagocytosis (in vitro phagocytosis assay).

For that purpose, bacterial *E. coli* clones are directly injected into mice and immune sera taken and tested in the relevant in vitro assay for functional opsonic or neutralizing antibodies. Alternatively, specific antibodies may be purified from human or mouse sera using peptides or proteins as substrate.

Host defence against *S. pyogenes* relies mainly on innate immunological mechanisms. Inducing high affinity antibodies of the opsonic and neutralizing type by vaccination helps the innate immune system to eliminate bacteria and toxins. This makes the method according to the present invention an optimal tool for the identification of group A streptococcal antigenic proteins.

The skin and mucous membranes are formidable barriers against invasion by streptococci. However, once the skin or the mucous membranes are breached the first line of non-adaptive cellular defence begins its co-ordinate action through complement and phagocytes, especially the polymorphonuclear leukocytes (PMNs). These cells can be regarded as the cornerstones in eliminating invading bacteria. As group A streptococci are primarily extracellular pathogens, the major anti-streptococcal adaptive response comes from the humoral arm of the immune system, and is mediated through three major mechanisms: promotion of opsonization, toxin neutralisation, and inhibition of adherence. It is believed that opsonization is especially important, because of its requirement for an effective phagocytosis. For efficient opsonization the microbial surface has to be coated with antibodies and complement factors for recognition by PMNs through receptors to the Fc fragment of the IgG molecule or to activated C3b. After opsonization, streptococci are phagocytosed and killed. Antibodies bound to specific antigens on the cell surface of bacteria serve as ligands for the attachment to PMNs and to promote phagocytosis. The very same antibodies bound to the adhesins and other cell surface proteins are expected to neutralize adhesion and prevent colonization. The selection of antigens as provided by the present invention is thus well suited to identify those that will lead to protection against infection in an animal model or in humans.

According to the antigen identification method used herein, the present invention can surprisingly provide a set of comprehensive novel nucleic acids and novel hyperimmune serum reactive antigens and fragments thereof of *S. pyogenes*, among other things, as described below. According to one aspect, the invention particularly relates to the nucleotide sequences encoding hyperimmune serum reactive antigens which sequences are set forth in the Sequence listing **Seq ID** No: 1-150 and the corresponding encoded amino acid sequences representing hyperimmune serum reactive antigens are set forth in the Sequence Listing **Seq ID** No 151-300.

In a preferred embodiment of the present invention, a nucleic acid molecule is provided which exhibit 70% identity over their entire length to a nucleotide sequence set forth with **Seq ID No** 1, 4-8, 10-18, 20,

22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150. Most highly preferred are nucleic acids that comprise a region that is at least 80% or at least 85% identical over their entire length to a nucleic acid molecule set forth with **Seq ID No** 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150. In this regard, nucleic acid molecules at least 90%, 91%, 92%, 93%, 94%, 95%, or 96% identical over their entire length to the same are particularly preferred. Furthermore, those with at least 97% are highly preferred, those with at least 98% and at least 99% are particularly highly preferred, with at least 99% or 99.5% being the more preferred, with 100% identity being especially preferred. Moreover, preferred embodiments in this respect are nucleic acids which encode hyperimmune serum reactive antigens or fragments thereof (polypeptides) which retain substantially the same biological function or activity as the mature polypeptide encoded by said nucleic acids set forth in the **Seq ID No** 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150.

Identity, as known in the art and used herein, is the relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as the case may be, as determined by the match between strings of such sequences. Identity can be readily calculated. While there exist a number of methods to measure identity between two polynucleotide or two polypeptide sequences, the term is well known to skilled artisans (e.g. *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987). Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity are codified in computer programs. Preferred computer program methods to determine identity between two sequences include, but are not limited to, GCG program package {Devereux, J. et al., 1984}, BLASTP, BLASTN, and FASTA {Altschul, S. et al., 1990}.

According to another aspect of the invention, nucleic acid molecules are provided which exhibit at least 96% identity to the nucleic acid sequence set forth with **Seq ID No** 64.

According to a further aspect of the present invention, nucleic acid molecules are provided which are identical to the nucleic acid sequences set forth with **Seq ID No** 3, 36, 47-48, 55, 62, 72, 80, 84, 95.

The nucleic acid molecules according to the present invention can as a second alternative also be a nucleic acid molecule which is at least essentially complementary to the nucleic acid described as the first alternative above. As used herein complementary means that a nucleic acid strand is base pairing via Watson-Crick base pairing with a second nucleic acid strand. Essentially complementary as used herein means that the base pairing is not occurring for all of the bases of the respective strands but leaves a certain number or percentage of the bases unpaired or wrongly paired. The percentage of correctly pairing bases is preferably at least 70 %, more preferably 80 %, even more preferably 90 % and most preferably any percentage higher than 90 %. It is to be noted that a percentage of 70 % matching bases is considered as homology and the hybridization having this extent of matching base pairs is considered as stringent. Hybridization conditions for this kind of stringent hybridization may be taken from Current Protocols in Molecular Biology (John Wiley and Sons, Inc., 1987). More particularly, the hybridization conditions can be as follows:

- Hybridization performed e.g. in 5 x SSPE, 5 x Denhardt's reagent, 0.1% SDS, 100 g/mL sheared DNA at 68°C
- Moderate stringency wash in 0.2xSSC, O.1% SDS at 42°C
- High stringency wash in 0.1xSSC, 0.1% SDS at 68°C

Genomic DNA with a GC content of 50% has an approximate T_M of 96°C. For 1% mismatch, the T_M is reduced by approximately 1°C.

In addition, any of the further hybridization conditions described herein are in principle applicable as well.

Of course, all nucleic acid sequence molecules which encode for the same polypeptide molecule as those identified by the present invention are encompassed by any disclosure of a given coding sequence, since the degeneracy of the genetic code is directly applicable to unambiguously determine all possible nucleic acid molecules which encode a given polypeptide molecule, even if the number of such degenerated nucleic acid molecules may be high. This is also applicable for fragments of a given polypeptide, as long as the fragments encode for a polypeptide being suitable to be used in a vaccination connection, e.g. as an active or passive vaccine.

The nucleic acid molecule according to the present invention can as a third alternative also be a nucleic acid which comprises a stretch of at least 15 bases of the nucleic acid molecule according to the first and second alternative of the nucleic acid molecules according to the present invention as outlined above. Preferably, the bases form a contiguous stretch of bases. However, it is also within the scope of the present invention that the stretch consists of two or more moieties which are separated by a number of bases.

The nucleic acid molecule according to the present invention can as a fourth alternative also be a nucleic acid molecule which anneals under stringent hybridisation conditions to any of the nucleic acids of the present invention according to the above outlined first, second, and third alternative. Stringent hybridisation conditions are typically those described herein.

Finally, the nucleic acid molecule according to the present invention can as a fifth alternative also be a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to any of the nucleic acid molecules according to any nucleic acid molecule of the present invention according to the first, second, third, and fourth alternative as outlined above. This kind of nucleic acid molecule refers to the fact that preferably the nucleic acids according to the present invention code for the hyperimmune serum reactive antigens or fragments thereof according to the present invention. This kind of nucleic acid molecule is particularly useful in the detection of a nucleic acid molecule according to the present invention and thus the diagnosis of the respective microorganisms such as *S. pyogenes* and any disease or diseased condition where this kind of microorganims is involved. Preferably, the hybridisation would occur or be preformed under stringent conditions as described in connection with the fourth alternative described above.

Nucleic acid molecule as used herein generally refers to any ribonucleic acid molecule or deoxyribonucleic acid molecule, which may be unmodified RNA or DNA or modified RNA or DNA. Thus, for instance, nucleic acid molecule as used herein refers to, among other, single-and double-stranded DNA, DNA that is a mixture of single- and double-stranded RNA, and RNA that is a mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded, or triple-stranded, or a mixture of single- and double-stranded regions. In addition, nucleic acid molecule as used herein refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The strands in such regions may be from the same molecule or from different molecules. The regions may include all of one or more of the molecules, but more typically involve only a region of some of the molecules. One of the molecules of a triple-helical region often is an oligonucleotide. As used herein, the term nucleic acid molecule includes DNAs or RNAs as described above that contain one or more modified bases. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are "nucleic acid molecule" as that term is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as tritylated bases, to name just two examples, are nucleic acid molecule as the term is used herein. It will be appreciated that a great variety of modifications have been made to DNA and RNA that serve many useful purposes known to those of skill in the art. The term nucleic acid molecule as it is employed herein

embraces such chemically, enzymatically or metabolically modified forms of nucleic acid molecule, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including simple and complex cells, *inter alia*. The term nucleic acid molecule also embraces short nucleic acid molecules often referred to as oligonucleotide(s). "Polynucleotide" and "nucleic acid" or "nucleic acid molecule" are often used interchangeably herein.

Nucleic acid molecules provided in the present invention also encompass numerous unique fragments, both longer and shorter than the nucleic acid molecule sequences set forth in the sequencing listing of the *S. pyogenes* coding regions, which can be generated by standard cloning methods. To be unique, a fragment must be of sufficient size to distinguish it from other known nucleic acid sequences, most readily determined by comparing any selected *S. pyogenes* fragment to the nucleotide sequences in computer databases such as GenBank.

Additionally, modifications can be made to the nucleic acid molecules and polypeptides that are encompassed by the present invention. For example, nucleotide substitutions can be made which do not affect the polypeptide encoded by the nucleic acid, and thus any nucleic acid molecule which encodes a hyperimmune serum reactive antigen or fragments thereof is encompassed by the present invention.

Furthermore, any of the nucleic acid molecules encoding hyperimmune serum reactive antigens or fragments thereof provided by the present invention can be functionally linked, using standard techniques such as standard cloning techniques, to any desired regulatory sequences, whether a *S. pyogenes* regulatory sequence or a heterologous regulatory sequence, heterologous leader sequence, heterologous marker sequence or a heterologous coding sequence to create a fusion protein.

Nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA or cRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The DNA may be triple-stranded, double-stranded or single-stranded. Single-stranded DNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand.

The present invention further relates to variants of the herein above described nucleic acid molecules which encode fragments, analogs and derivatives of the hyperimmune serum reactive antigens and fragments thereof having a deducted *S. pyogenes* amino acid sequence set forth in the Sequence Listing. A variant of the nucleic acid molecule may be a naturally occurring variant such as a naturally occurring allelic variant, or it may be a variant that is not known to occur naturally. Such non-naturally occurring variants of the nucleic acid molecule may be made by mutagenesis techniques, including those applied to nucleic acid molecules, cells or organisms.

Among variants in this regard are variants that differ from the aforementioned nucleic acid molecules by nucleotide substitutions, deletions or additions. The substitutions, deletions or additions may involve one or more nucleotides. The variants may be altered in coding or non-coding regions or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Preferred are nucleic acid molecules encoding a variant, analog, derivative or fragment, or a variant, analogue or derivative of a fragment, which have a *S. pyogenes* sequence as set forth in the Sequence Listing, in which several, a few, 5 to 10, 1 to 5, 1 to 3, 2, 1 or no amino acid(s) is substituted, deleted or added, in any combination. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the *S. pyogenes* polypeptides set forth in the Sequence Listing. Also especially preferred in this regard are conservative substitutions.

The peptides and fragments according to the present invention also include modified epitopes wherein preferably one or two of the amino acids of a given epitope are modified or replaced according to the

rules disclosed in e.g. {Tourdot, S. et al., 2000}, as well as the nucleic acid sequences encoding such modified epitopes.

It is clear that also epitopes derived from the present epitopes by amino acid exchanges improving, conserving or at least not significantly impeding the T cell activating capability of the epitopes are covered by the epitopes according to the present invention. Therefore the present epitopes also cover epitopes, which do not contain the original sequence as derived from *S. pyogenes*, but trigger the same or preferably an improved T cell response. These epitope are referred to as "heteroclitic"; they need to have a similar or preferably greater affinity to MHC/HLA molecules, and the need the ability to stimulate the T cell receptors (TCR) directed to the original epitope in a similar or preferably stronger manner.

Heteroclitic epitopes can be obtained by rational design i.e. taking into account the contribution of individual residues to binding to MHC/HLA as for instance described by {Rammensee, H. et al., 1999}, combined with a systematic exchange of residues potentially interacting with the TCR and testing the resulting sequences with T cells directed against the original epitope. Such a design is possible for a skilled man in the art without much experimentation.

Another possibility includes the screening of peptide libraries with T cells directed against the original epitope. A preferred way is the positional scanning of synthetic peptide libraries. Such approaches have been described in detail for instance by {Hemmer, B. et al., 1999}and the references given therein.

As an alternative to epitopes represented by the present derived amino acid sequences or heteroclitic epitopes, also substances mimicking these epitopes e.g. "peptidemimetica" or "retro-inverso-peptides" can be applied.

Another aspect of the design of improved epitopes is their formulation or modification with substances increasing their capacity to stimulate T cells. These include T helper cell epitopes, lipids or liposomes or preferred modifications as described in WO 01/78767.

Another way to increase the T cell stimulating capacity of epitopes is their formulation with immune stimulating substances for instance cytokines or chemokines like interleukin-2, -7, -12, -18, class I and II interferons (IFN), especially IFN-gamma, GM-CSF, TNF-alpha, flt3-ligand and others.

As discussed additionally herein regarding nucleic acid molecule assays of the invention, for instance, nucleic acid molecules of the invention as discussed above, may be used as a hybridization probe for RNA, cDNA and genomic DNA to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes that have a high sequence similarity to the nucleic acid molecules of the present invention. Such probes generally will comprise at least 15 bases. Preferably, such probes will have at least 20, at least 25 or at least 30 bases, and may have at least 50 bases. Particularly preferred probes will have at least 30 bases, and will have 50 bases or less, such as 30, 35, 40, 45, or 50 bases.

For example, the coding region of a nucleic acid molecule of the present invention may be isolated by screening a relevant library using the known DNA sequence to synthesize an oligonucleotide probe. A labeled oligonucleotide having a sequence complementary to that of a gene of the present invention is then used to screen a library of cDNA, genomic DNA or mRNA to determine to which members of the library the probe hybridizes.

The nucleic acid molecules and polypeptides of the present invention may be employed as reagents and materials for development of treatments of and diagnostics for disease, particularly human disease, as further discussed herein relating to nucleic acid molecule assays, *inter alia*.

The nucleic acid molecules of the present invention that are oligonucleotides can be used in the processes herein as described, but preferably for PCR, to determine whether or not the *S. pyogenes* genes identified herein in whole or in part are present and/or transcribed in infected tissue such as blood. It is recognized that such sequences will also have utility in diagnosis of the stage of infection and type of infection the pathogen has attained. For this and other purposes the arrays comprising at least one of the nucleic acids according to the present invention as described herein, may be used.

The nucleic acid molecules according to the present invention may be used for the detection of nucleic acid molecules and organisms or samples containing these nucleic acids. Preferably such detection is for diagnosis, more preferable for the diagnosis of a disease related or linked to the present or abundance of *S. pyogenes.*

Eukaryotes (herein also "individual(s)"), particularly mammals, and especially humans, infected with *S. pyogenes* may be detected at the DNA level by a variety of techniques. Preferred candidates for distinguishing a *S. pyogenes* from other organisms can be obtained.

The invention provides a process for diagnosing disease, arising from infection with *S. pyogenes*, comprising determining from a sample isolated or derived from an individual an increased level of expression of a nucleic acid molecule having the sequence of a nucleic acid molecule set forth in the Sequence Listing. Expression of nucleic acid molecules can be measured using any one of the methods well known in the art for the quantitation of nucleic acid molecules, such as, for example, PCR, RT-PCR, Rnase protection, Northern blotting, other hybridisation methods and the arrays described herein.

Isolated as used herein means separated "by the hand of man" from its natural state; i.e., that, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a naturally occurring nucleic acid molecule or a polypeptide naturally present in a living organism in its natural state is not "isolated," but the same nucleic acid molecule or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. As part of or following isolation, such nucleic acid molecules can be joined to other nucleic acid molecules, such as DNAs, for mutagenesis, to form fusion proteins, and for propagation or expression in a host, for instance. The isolated nucleic acid molecules, alone or joined to other nucleic acid molecules such as vectors, can be introduced into host cells, in culture or in whole organisms. Introduced into host cells in culture or in whole organisms, such DNAs still would be isolated, as the term is used herein, because they would not be in their naturally occurring form or environment. Similarly, the nucleic acid molecules and polypeptides may occur in a composition, such as a media formulations, solutions for introduction of nucleic acid molecules or polypeptides, for example, into cells, compositions or solutions for chemical or enzymatic reactions, for instance, which are not naturally occurring compositions, and, therein remain isolated nucleic acid molecules or polypeptides within the meaning of that term as it is employed herein.

The nucleic acids according to the present invention may be chemically synthesized. Alternatively, the nucleic acids can be isolated from *S. pyogenes* by methods known to the one skilled in the art.

According to another aspect of the present invention, a comprehensive set of novel hyperimmune serum reactive antigens and fragments thereof are provided by using the herein described antigen identification method. In a preferred embodiment of the invention, a hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by any one of the nucleic acids molecules herein described and fragments thereof are provided. In another preferred embodiment of the invention a novel set of hyperimmune serum-reactive antigens which comprises amino acid sequences selected from a group consisting of the polypeptide sequences as represented in **Seq ID No** 151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244 and 246-300 and fragments thereof are provided. In a further preferred embodiment of the invention hyperimmune serum-reactive antigens which comprise amino acid sequences selected from a group

consisting of the polypeptide sequences as represented in **Seq ID No**214 and fragments thereof are provided. In a still preferred embodiment of the invention hyperimmune serum-reactive antigens which comprise amino acid sequences selected from a group consisting of the polypeptide sequences as represented in **Seq ID No** 153, 186, 197-198, 205, 212, 222, 230, 234, 245. and fragments thereof are provided.

The hyperimmune serum reactive antigens and fragments thereof as provided in the invention include any polypeptide set forth in the Sequence Listing as well as polypeptides which have at least 70% identity to a polypeptide set forth in the Sequence Listing, preferably at least 80% or 85% identity to a polypeptide set forth in the Sequence Listing, and more preferably at least 90% similarity (more preferably at least 90% identity) to a polypeptide set forth in the Sequence Listing and still more preferably at least 95%, 96%, 97%, 98%, 99% or 99.5% similarity (still more preferably at least 95%, 96%, 97%, 98%, 99%, or 99.5% identity) to a polypeptide set forth in the Sequence Listing and also include portions of such polypeptides with such portion of the polypeptide generally containing at least 4 amino acids and more preferably at least 8, still more preferably at least 30, still more preferably at least 50 amino acids, such as 4, 8, 10, 20, 30, 35, 40, 45 or 50 amino acids.

The invention also relates to fragments, analogs, and derivatives of these hyperimmune serum reactive antigens and fragments thereof. The terms "fragment", "derivative" and "analog" when referring to an antigen whose amino acid sequence is set forth in the Sequence Listing, means a polypeptide which retains essentially the same biological function or activity as such hyperimmune serum reactive antigen and fragment thereof.

The fragment, derivative or analog of a hyperimmune serum reactive antigen and fragment thereof may be 1) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or 2) one in which one or more of the amino acid residues includes a substituent group, or 3) one in which the mature hyperimmune serum reactive antigen or fragment thereof is fused with another compound, such as a compound to increase the half-life of the hyperimmune serum reactive antigen and fragment thereof (for example, polyethylene glycol), or 4) one in which the additional amino acids are fused to the mature hyperimmune serum reactive antigen or fragment thereof, such as a leader or secretory sequence or a sequence which is employed for purification of the mature hyperimmune serum reactive antigen or fragment thereof or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

The present invention also relates to antigens of different S. pyogenes isolates. Such homologues may easily be isolated based on the nucleic acid and amino acid sequences disclosed herein. There are more than 80 M protein serotypes distinguished to date and the typing is based on the variable region at the 5'end of the emm gene (see e.g. Vitali et al. 2002). The presence of any antigen can accordingly be determined for every M serotype. In addition it is possible to determine the variability of a particular antigen in the various M serotypes as described for the sic gene (Hoe et al., 2001). The influence of the various M serotypes on the kind of disease it causes is summarized in a recent review (Cunningham, 2000). In particular, two groups of serotypes can be distinguished:
1) Those causing Pharyngitis and Scarlet fever (e.g. M types 1, 3, 5, 6, 14, 18, 19, 24)
2) Those causing Pyoderma and Streptococcal skin infections (e.g. M types 2, 49, 57, 59, 60, 61)
This can serve as the basis to identify the relevance of an antigen for the use as a vaccine or in general as a drug targeting a specific disease.

The information e.g. from the homepage of the CDC (http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm) gives a dendrogram showing the relatedness of various M serotypes. Further relevant references are Vitali et al., Journal of Clinical Microbiology

40:679-681. (2002) (molecular emm typing method), Enright et al., Infection and Immunity 69:2416-2427. (2001) (alternative molecular typing method (MLST)) , Hoe et al., The Journal of Infectious Diseases 183:633-639. (2001)(example for the variation of one antigen (sic) in many different serotypes) and Cunningham, CLINICAL MICROBIOLOGY REVIEWS 13:470–511. (2000)(review on GAS pathogenesis). All emm types are completely listed and may be downloaded from the above mentioned address.

The dendrogram was constructed by sequential use of the Wisconsin Package Version 10.1, Genetics Computer Group (GCG), Madison programs Pileup, Distances, and Growtree. Basically, 22 residues of signal sequence plus 83 additional N terminal residues were used for the alignments which include selected sequences from the database. The selected sequences include new emm designations 103-124 (described in table below) as well as their closest "classical" M protein matches. Although this analysis is limited in that the C terminal ends are truncated arbitrarily, this is a typical result in that the dendrogram separates clusters of opacity factor positive strain M sequences from opacity factor strain negative M sequences.

emm type/previous designation - GenBank accession number - Countries where isolated - Closest N-terminal M protein sequence match (% identity):

emm103/st2034 U74320 PNG, Bra, Egy, Mal,Nep, NZ, US M87 (66%)
emm104/st2034 AF056300 PNG, Egy, Mal,Nep, NZ, US M66 (72%)
emm105/st4529 AF060227 Mal, Nep, NZ, US M5 (45%)
emm106/st4532 AF077666 Mal, Egy, Iran,Nep M27G (71%)
emm107/st4264 AF163686 Mal, NZ M25 (52%)
emm108/st4547 AF052426 Mal, Bra, Egy, Ira, NZ M70 (84%) emm109/st3018 AF077667 Mal, Egy, NZ M28(74%)
emm110/st4935 U92492 Ind, Bul, NZ, Rus, US M13 (60%)
emm111/st4973 AF128960 Ind, Bra, Nep, US M80 (40%)
emm112/stCmuk16 AF091806 Thi, Bra, Rus, US M27L/77 (59%) emm113/st2267 AF078068 NZ, Thai, Chi M13 (50%)
emm114/st2967 U50338 US, Can, Gam, NZ, PNG M73 (80%)
emm115/st2980 AF028712 US, Bra, Rus M36 (64%)
emm116/st2370 AF156180 US, Nep, NZ M52 (60%)
emm117/st436 AF058801 US M13 (59%)
emm118/st448 AF058802 US, Bra, Egy, Nep, NZ M49 (79%)
emm119/st3365 AF083874 US, Br, Nep M52 (59%)
emm120/st1135 AF296181 Egy M56 (78%)
emm121/st1161 AF296182 Egy M64 (64%)
emm122/st1432 AF222860 Egy, Rus, Nep M18 (40%)
emm123/st6949AF213451Arg, US, NZM80 (68%)
st1160/emm124AF149048 and AF018178Egy, Mal, NZM2 (82%)

Abbreviations: Arg, Argentina; Bra, Brazil; Bul, Bulgaria; Can, Canada; Chi, Chile; Egy, Egypt; Gam, Gambia; Ind, India; Ira, Iran; Mal, Malaysia; Nep, Nepal; NZ, New Zealand; PNG, Papua New Guinea; Thi, Thailand; Rus, Russia; US, United States. %: Closest mature M protein sequence match to predicted 50 mature N terminal residuesfrom serologically characterized Lancefield type.

emm types and sequence types:

In many cases the emm sequence reference strains came directly from the M type collection of Dr. Rebecca Lancefield. Such strains are designated RCL.

The sequences starting with "emm" indicate that isolates represented by this type have been analyzed by several reference laboratories besides the CDC streptococcal laboratories. Each of the "new" emm types

emm94 through emm124 are represented by multiple independent isolates recovered from serious disease manifestations, are M protein nontypeable with all typing sera stocks available to international GAS reference laboratories, and demonstrate antiphagocytic properties in vitro by multiplying in normal human blood. Strains with emm sequences starting with "st" (sequence type) have not yet been completely validated by all of the reference laboratories.

GAS Genetics:

It has long been known that antiserum against serum opacity factor positive (SOF+) strains inhibits OF activity in a strain-specific manner. Therefore, 500-2700 base variable regions of the sof (serum opacity factor) gene representing at least 60 distinct sof genes were analysed from GAS opacity factor positive strains (and interestingly, a homolog commonly found in OF negative emm12 isolates and emm/M type 12 reference strain). It was found that sof gene sequences are also remarkably variable among the different GAS strains, although usually well conserved within an emm type. Important strains include therefore emm1, emm100, emm101, emm102, emm103, emm104, emm105, emm106, emm107, emm108, emm109, emm11, emm110, emm111, emm112, emm113, emm114, emm115, emm116, emm117, emm118, emm119, emm12, emm120, emm121, emm122, emm123, emm124, emm13L, emm14, emm15, emm17, emm18, emm19, emm2, emm22, emm23, emm24, emm25, emm26, emm27G, emm28, emm29, emm3, emm30, emm31, emm32, emm33, emm34, emm36, emm37, emm38, emm39, emm4, emm40, emm41, emm42, emm43, emm44, emm46, emm47, emm48, emm49, emm5, emm50, emm51, emm52, emm53, emm54, emm55, emm56, emm57, emm58, emm59, emm6, emm60, emm61 , emm62 , emm63, emm64, emm65, emm66, emm67, emm68,mm69, emm70, emm71, emm72, emm73, emm74, emm75, emm76, emm77, emm78, emm79, emm8, emm80, emm81 , emm82, emm83, emm84, emm85, emm86, emm87, emm88, emm89, emm9, emm90, emm91, emm92,emm93, emm94, emm95, emm96, emm97, emm98, emm99 ,st1389,st1731,st1759,st1815 , st1967, st1969, st1rp31, st11014, st2037, st204, st211, st213, st2147, st1207, st245, st2460, st2461, st2463, st2904, st2911, st2917, st2926, st2940, st369, st3757, st3765, st3850, st5282, st6735, st7700, st809,st833,st854 , st980584, stck249, stck401, std432, std631, std633, stIL103, stIL62, stns292, stns554, sts104, stc1400, stc1741, stc36, stc3852, stc5344, stc5345, stc57, stc6979, stc74a, stc839, stg10, stg11, stg1389, stg166b, stg1750, stg2078, stg3390, stg4222, stg4545, stg480, stg4831, stg485, stg4974, stg5063, stg6, stg62647, stg643, stg652, stg653, stg663, stg840, stg93464, stg97, stL1376, stL1929 and stL2764.

Among the particularly preferred embodiments of the invention in this regard are the hyperimmune serum reactive antigens set forth in the Sequence Listing, variants, analogs, derivatives and fragments thereof, and variants, analogs and derivatives of fragments. Additionally, fusion polypeptides comprising such hyperimmune serum reactive antigens, variants, analogs, derivatives and fragments thereof, and variants, analogs and derivatives of the fragments are also encompassed by the present invention. Such fusion polypeptides and proteins, as well as nucleic acid molecules encoding them, can readily be made using standard techniques, including standard recombinant techniques for producing and expression a recombinant polynucleic acid encoding a fusion protein.

Among preferred variants are those that vary from a reference by conservative amino acid substitutions. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe and Tyr.

Further particularly preferred in this regard are variants, analogs, derivatives and fragments, and variants, analogs and derivatives of the fragments, having the amino acid sequence of any polypeptide set forth in the Sequence Listing, in which several, a few, 5 to 10, 1 to 5, 1 to 3, 2, 1 or no amino acid residues are substituted, deleted or added, in any combination. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the

polypeptide of the present invention. Also especially preferred in this regard are conservative substitutions. Most highly preferred are polypeptides having an amino acid sequence set forth in the Sequence Listing without substitutions. Specifically suitable amino acid substitutions are those which are contained in homologues for the sequences disclosed in the Sequence Listing according to the present application. A suitable sequence derivative of an antigen or epitope as disclosed herein therefore includes one or more variations being present in one or more strains or serotypes of S. pyogenes (preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid exchanges which are based on such homolog variations). Such antigens comprise sequences which may be naturally occurring sequences or newly created artificial sequences. These preferred antigen variants are based on such naturally occurring sequence variations, e.g. forming a "master sequence" for the antigenic regions of the polypeptides according to the present invention. Suitable examples for such homolog variations or exchanges are given in table 5 in the example section. For example, a given S.pyogenes sequence may be amended by including such one or more variations thereby creating an artificial (i.e. non-naturally occurring) variant of this given (naturally occurring) antigen or epitope sequence.

The hyperimmune serum reactive antigens and fragments thereof of the present invention are preferably provided in an isolated form, and preferably are purified to homogeneity.

Also among preferred embodiments of the present invention are polypeptides comprising fragments of the polypeptides having the amino acid sequence set forth in the Sequence Listing, and fragments of variants and derivatives of the polypeptides set forth in the Sequence Listing.

In this regard a fragment is a polypeptide having an amino acid sequence that entirely is the same as part but not all of the amino acid sequence of the afore mentioned hyperimmune serum reactive antigen and fragment thereof, and variants or derivative, analogs, fragments thereof. Such fragments may be "free-standing", i.e., not part of or fused to other amino acids or polypeptides, or they may be comprised within a larger polypeptide of which they form a part or region. Also preferred in this aspect of the invention are fragments characterised by structural or functional attributes of the polypeptide of the present invention, i.e. fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta-amphipathic regions, flexible regions, surface-forming regions, substrate binding regions, and high antigenic index regions of the polypeptide of the present invention, and combinations of such fragments. Preferred regions are those that mediate activities of the hyperimmune serum reactive antigens and fragments thereof of the present invention. Most highly preferred in this regard are fragments that have a chemical, biological or other activity of the hyperimmune serum reactive antigen and fragments thereof of the present invention, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Particularly preferred are fragments comprising receptors or domains of enzymes that confer a function essential for viability of *S. pyogenes* or the ability to cause disease in humans. Further preferred polypeptide fragments are those that comprise or contain antigenic or immunogenic determinants in an animal, especially in a human.

An antigenic fragment is defined as a fragment of the identified antigen which is for itself antigenic or may be made antigenic when provided as a hapten. Therefore, also antigens or antigenic fragments showing one or (for longer fragments) only a few amino acid exchanges are enabled with the present invention, provided that the antigenic capacities of such fragments with amino acid exchanges are not severely deteriorated on the exchange(s), i.e., suited for eliciting an appropriate immune response in an individual vaccinated with this antigen and identified by individual antibody preparations from individual sera.

Preferred examples of such fragments of a hyperimmune serum-reactive antigen are selected from the group consisting of peptides comprising amino acid sequences of column "predicted immunogenic aa",

and "Location of identified immunogenic region" of Table 1; the serum reactive epitopes of Table 2, especially peptides comprising amino acid 4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425 and 1-114 of **Seq ID No** 151; 5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395 and 29-226 of **Seq ID No** 152; 4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254 and 919-929 of **Seq ID No** 153; 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179-198 of **Seq ID No** 211; 27-51 of **Seq ID No** 213; 46-70 of **Seq ID No** 213; 65-89 of **Seq ID No** 213; 84-108 of **Seq ID No** 213; 112-141 of **Seq ID No** 213; 248-260 of **Seq ID No** 215; 59-78 of **Seq ID No** 216; 154-170 of **Seq ID No** 218; 57-73 of **Seq ID No** 219; 297-314 of **Seq ID No** 220; 142-157 of **Seq ID No** 221; 428-447 of **Seq ID No** 222; 573-593 of **Seq ID No** 222; 523-544 of **Seq ID No** 223; 46-70 of **Seq ID No** 223; 65-89 of **Seq ID No** 223; 84-108 of **Seq ID No** 223; 122-151 of **Seq ID No** 223; 123-142 of **Seq ID No** 224; 903-921 of **Seq ID No** 225; 119-136 of **Seq ID No** 226; 142-161 of **Seq ID No** 227; 258-277 of **Seq ID No** 228; 272-300 of **Seq ID No** 228; 295-322 of **Seq ID No** 228; 311-343 of **Seq ID No** 229; 278-304 of **Seq ID No** 229; 131-150 of **Seq ID No** 230; 195-218 of **Seq ID No** 230; 53-70 of **Seq ID No** 231; 184-208 of **Seq ID No** 232; 222-246 of **Seq ID No** 232; 241-265 of **Seq ID No** 232; 260-284 of **Seq ID No** 232; 279-303 of **Seq ID No** 232; 317-341 of **Seq ID No** 232; 678-696 of **Seq ID No** 233; 88-114 of **Seq ID No** 235; 464-481 of **Seq ID No** 235; 153-172 of **Seq ID No** 236; 137-155, 166-184 of **Seq ID No** 236; 215-228 of **Seq ID No** 236; 37-51 of **Seq ID No** 237; 53-75 of **Seq ID No** 237; 232-251 of **Seq ID No** 237; 318-336 of **Seq ID No** 237; 305-315 of **Seq ID No** 238; 131-156 of **Seq ID No** 238; 258-275 of **Seq ID No** 241; 107-137 of **Seq ID No** 243; 138-162 of **Seq ID No** 243; 157-181 of **Seq ID No** 243; 195-227 of **Seq ID No** 243; 62-78 of **Seq ID No** 244; 567-584 of **Seq ID No** 245, and fragments comprising at least 6, preferably more than 8, especially more than 10 aa of said sequences. All these fragments individually and each independently form a preferred selected aspect of the present invention.

All linear hyperimmune serum reactive fragments of a particular antigen may be identified by analysing the entire sequence of the protein antigen by a set of peptides overlapping by 1 amino acid with a length of at least 10 amino acids. Subsequently, non-linear epitopes can be identified by analysis of the protein antigen with hyperimmune sera using the expressed full-length protein or domain polypeptides thereof. Assuming that a distinct domain of a protein is sufficient to form the 3D structure independent from the native protein, the analysis of the respective recombinant or synthetically produced domain polypeptide with hyperimmune serum would allow the identification of conformational epitopes within the individual domains of multi-domain proteins. For those antigens where a domain possesses linear as well as conformational epitopes, competition experiments with peptides corresponding to the linear epitopes may be used to confirm the presence of conformational epitopes.

It will be appreciated that the invention also relates to, among others, nucleic acid molecules encoding the aforementioned fragments, nucleic acid molecules that hybridise to nucleic acid molecules encoding the fragments, particularly those that hybridise under stringent conditions, and nucleic acid molecules, such as PCR primers, for amplifying nucleic acid molecules that encode the fragments. In these regards, preferred nucleic acid molecules are those that correspond to the preferred fragments, as discussed above.

The present invention also relates to vectors which comprise a nucleic acid molecule or nucleic acid molecules of the present invention, host cells which are genetically engineered with vectors of the invention and the production of hyperimmune serum reactive antigens and fragments thereof by recombinant techniques.

A great variety of expression vectors can be used to express a hyperimmune serum reactive antigen or fragment thereof according to the present invention. Generally, any vector suitable to maintain, propagate or express nucleic acids to express a polypeptide in a host may be used for expression in this regard. In accordance with this aspect of the invention the vector may be, for example, a plasmid vector, a single or double-stranded phage vector, a single or double-stranded RNA or DNA viral vector. Starting plasmids disclosed herein are either commercially available, publicly available, or can be constructed from available plasmids by routine application of well-known, published procedures. Preferred among vectors, in certain respects, are those for expression of nucleic acid molecules and hyperimmune serum reactive antigens or fragments thereof of the present invention. Nucleic acid constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the hyperimmune serum reactive antigens and fragments thereof of the invention can be synthetically produced by conventional peptide synthesizers. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA construct of the present invention.

Host cells can be genetically engineered to incorporate nucleic acid molecules and express nucleic acid molecules of the present invention. Representative examples of appropriate hosts include bacterial cells, such as streptococci, staphylococci, *E. coli*, *Streptomyces* and *Bacillus subtillis cells*; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, Hela, C127, 3T3, BHK, 293 and Bowes melanoma cells; and plant cells.

The invention also provides a process for producing a *S. pyogenes* hyperimmune serum reactive antigen and a fragment thereof comprising expressing from the host cell a hyperimmune serum reactive antigen or fragment thereof encoded by the nucleic acid molecules provided by the present invention. The invention further provides a process for producing a cell, which expresses a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof comprising transforming or transfecting a suitable host cell with the vector according to the present invention such that the transformed or transfected cell expresses

the polypeptide encoded by the nucleic acid contained in the vector.

The polypeptide may be expressed in a modified form, such as a fusion protein, and may include not only secretion signals but also additional heterologous functional regions. Thus, for instance, a region of additional amino acids, particularly charged amino acids, may be added to the N- or C-terminus of the polypeptide to improve stability and persistence in the host cell, during purification or during subsequent handling and storage. Also, regions may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability or to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize or purify polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobin molecules together with another protein or part thereof. In drug discovery, for example, proteins have been fused with antibody Fc portions for the purpose of high-throughout screening assays to identify antagonists. See for example, {Bennett, D. et al., 1995} and {Johanson, K. et al., 1995}.

The *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography.

The hyperimmune serum reactive antigens and fragments thereof according to the present invention can be produced by chemical synthesis as well as by biotechnological means. The latter comprise the transfection or transformation of a host cell with a vector containing a nucleic acid according to the present invention and the cultivation of the transfected or transformed host cell under conditions which are known to the ones skilled in the art. The production method may also comprise a purification step in order to purify or isolate the polypeptide to be manufactured. In a preferred embodiment the vector is a vector according to the present invention.

The hyperimmune serum reactive antigens and fragments thereof according to the present invention may be used for the detection of the organism or organisms in a sample containing these organisms or polypeptides derived thereof. Preferably such detection is for diagnosis, more preferable for the diagnosis of a disease, most preferably for the diagnosis of a diseases related or linked to the presence or abundance of Gram-positive bacteria, especially bacteria selected from the group comprising streptococci, staphylococci and lactococci. More preferably, the microorganisms are selected from the group comprising *Streptococcus agalactiae*, *Streptococcus pneumoniae* and *Streptococcus mutans*, especially the microorganism is *Streptococcus pyogenes.*

The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of the hyperimmune serum reactive antigens and fragments thereof of the present invention in cells and tissues, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of the polypeptide compared to normal control tissue samples may be used to detect the presence of an infection, for example, and to identify the infecting organism. Assay techniques that can be used to determine levels of a polypeptide, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Among these, ELISAs frequently are preferred. An ELISA assay initially comprises preparing an antibody specific to the polypeptide, preferably a monoclonal antibody. In addition, a reporter antibody generally is prepared which binds to the monoclonal antibody. The reporter antibody is attached to a

detectable reagent such as radioactive, fluorescent or enzymatic reagent, such as horseradish peroxidase enzyme.

The hyperimmune serum reactive antigens and fragments thereof according to the present invention may also be used for the purpose of or in connection with an array. More particularly, at least one of the hyperimmune serum reactive antigens and fragments thereof according to the present invention may be immobilized on a support. Said support typically comprises a variety of hyperimmune serum reactive antigens and fragments thereof whereby the variety may be created by using one or several of the hyperimmune serum reactive antigens and fragments thereof according to the present invention and/or hyperimmune serum reactive antigens and fragments thereof being different. The characterizing feature of such array as well as of any array in general is the fact that at a distinct or predefined region or position on said support or a surface thereof, a distinct polypeptide is immobilized. Because of this any activity at a distinct position or region of an array can be correlated with a specific polypeptide. The number of different hyperimmune serum reactive antigens and fragments thereof immobilized on a support may range from as little as 10 to several 1000 different hyperimmune serum reactive antigens and fragments thereof. The density of hyperimmune serum reactive antigens and fragments thereof per cm^2 is in a preferred embodiment as little as 10 peptides/polypeptides per cm^2 to at least 400 different peptides/polypeptides per cm^2 and more particularly at least 1000 different hyperimmune serum reactive antigens and fragments thereof per cm^2.

The manufacture of such arrays is known to the one skilled in the art and, for example, described in US patent 5,744,309. The array preferably comprises a planar, porous or non-porous solid support having at least a first surface. The hyperimmune serum reactive antigens and fragments thereof as disclosed herein, are immobilized on said surface. Preferred support materials are, among others, glass or cellulose. It is also within the present invention that the array is used for any of the diagnostic applications described herein. Apart from the hyperimmune serum reactive antigens and fragments thereof according to the present invention also the nucleic acid molecules according to the present invention may be used for the generation of an array as described above. This applies as well to an array made of antibodies, preferably monoclonal antibodies as, among others, described herein.

In a further aspect the present invention relates to an antibody directed to any of the hyperimmune serum reactive antigens and fragments thereof, derivatives or fragments thereof according to the present invention. The present invention includes, for example, monoclonal and polyclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of a Fab expression library. It is within the present invention that the antibody may be chimeric, i. e. that different parts thereof stem from different species or at least the respective sequences are taken from different species.

Antibodies generated against the hyperimmune serum reactive antigens and fragments thereof corresponding to a sequence of the present invention can be obtained by direct injection of the hyperimmune serum reactive antigens and fragments thereof into an animal or by administering the hyperimmune serum reactive antigens and fragments thereof to an animal, preferably a non-human. The antibody so obtained will then bind the hyperimmune serum reactive antigens and fragments thereof itself. In this manner, even a sequence encoding only a fragment of a hyperimmune serum reactive antigen and fragments thereof can be used to generate antibodies binding the whole native hyperimmune serum reactive antigen and fragments thereof. Such antibodies can then be used to isolate the hyperimmune serum reactive antigens and fragments thereof from tissue expressing those hyperimmune serum reactive antigens and fragments thereof.

For preparation of monoclonal antibodies, any technique known in the art which provides antibodies produced by continuous cell line cultures can be used. (as described originally in {Kohler, G. et al., 1975}.

Techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778) can be

adapted to produce single chain antibodies to immunogenic hyperimmune serum reactive antigens and fragments thereof according to this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies to immunogenic hyperimmune serum reactive antigens and fragments thereof according to this invention.

Alternatively, phage display technology or ribosomal display could be utilized to select antibody genes with binding activities towards the hyperimmune serum reactive antigens and fragments thereof either from repertoires of PCR amplified v-genes of lymphocytes from humans screened for possessing respective target antigens or from naïve libraries {McCafferty, J. et al., 1990}; {Marks, J. et al., 1992}. The affinity of these antibodies can also be improved by chain shuffling {Clackson, T. et al., 1991}.

If two antigen binding domains are present, each domain may be directed against a different epitope – termed 'bispecific' antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the hyperimmune serum reactive antigens and fragments thereof or purify the hyperimmune serum reactive antigens and fragments thereof of the present invention by attachment of the antibody to a solid support for isolation and/or purification by affinity chromatography.

Thus, among others, antibodies against the hyperimmune serum reactive antigens and fragments thereof of the present invention may be employed to inhibit and/or treat infections, particularly bacterial infections and especially infections arising from *S. pyogenes*.

Hyperimmune serum reactive antigens and fragments thereof include antigenically, epitopically or immunologically equivalent derivatives which form a particular aspect of this invention. The term "antigenically equivalent derivative" as used herein encompasses a hyperimmune serum reactive antigen and fragments thereof or its equivalent which will be specifically recognized by certain antibodies which, when raised to the protein or hyperimmune serum reactive antigen and fragments thereof according to the present invention, interfere with the interaction between pathogen and mammalian host. The term "immunologically equivalent derivative" as used herein encompasses a peptide or its equivalent which when used in a suitable formulation to raise antibodies in a vertebrate, the antibodies act to interfere with the interaction between pathogen and mammalian host.

The hyperimmune serum reactive antigens and fragments thereof, such as an antigenically or immunologically equivalent derivative or a fusion protein thereof can be used as an antigen to immunize a mouse or other animal such as a rat or chicken. The fusion protein may provide stability to the hyperimmune serum reactive antigens and fragments thereof. The antigen may be associated, for example by conjugation, with an immunogenic carrier protein, for example bovine serum albumin (BSA) or keyhole limpet haemocyanin (KLH). Alternatively, an antigenic peptide comprising multiple copies of the protein or hyperimmune serum reactive antigen and fragments thereof, or an antigenically or immunologically equivalent hyperimmune serum reactive antigen and fragments thereof, may be sufficiently antigenic to improve immunogenicity so as to obviate the use of a carrier.

Preferably the antibody or derivative thereof is modified to make it less immunogenic in the individual. For example, if the individual is human the antibody may most preferably be "humanized", wherein the complimentarity determining region(s) of the hybridoma-derived antibody has been transplanted into a human monoclonal antibody, for example as described in {Jones, P. et al., 1986} or {Tempest, P. et al., 1991}.

The use of a polynucleotide of the invention in genetic immunization will preferably employ a suitable delivery method such as direct injection of plasmid DNA into muscle, delivery of DNA complexed with specific protein carriers, coprecipitation of DNA with calcium phosphate, encapsulation of DNA in

various forms of liposomes, particle bombardment {Tang, D. et al., 1992}, {Eisenbraun, M. et al., 1993} and *in vivo* infection using cloned retroviral vectors {Seeger, C. et al., 1984}.

In a further aspect the present invention relates to a peptide binding to any of the hyperimmune serum reactive antigens and fragments thereof according to the present invention, and a method for the manufacture of such peptides whereby the method is characterized by the use of the hyperimmune serum reactive antigens and fragments thereof according to the present invention and the basic steps are known to the one skilled in the art.

Such peptides may be generated by using methods according to the state of the art such as phage display or ribosome display. In case of phage display, basically a library of peptides is generated, in form of phages, and this kind of library is contacted with the target molecule, in the present case a hyperimmune serum reactive antigen and fragments thereof according to the present invention. Those peptides binding to the target molecule are subsequently removed, preferably as a complex with the target molecule, from the respective reaction. It is known to the one skilled in the art that the binding characteristics, at least to a certain extent, depend on the particularly realized experimental set-up such as the salt concentration and the like. After separating those peptides binding to the target molecule with a higher affinity or a bigger force, from the non-binding members of the library, and optionally also after removal of the target molecule from the complex of target molecule and peptide, the respective peptide(s) may subsequently be characterised. Prior to the characterisation optionally an amplification step is realized such as, e. g. by propagating the peptide coding phages. The characterisation preferably comprises the sequencing of the target binding peptides. Basically, the peptides are not limited in their lengths, however, preferably peptides having a lengths from about 8 to 20 amino acids are preferably obtained in the respective methods. The size of the libraries may be about 10^2 to 10^{18}, preferably 10^8 to 10^{15} different peptides, however, is not limited thereto.

A particular form of target binding hyperimmune serum reactive antigens and fragments thereof are the so-called "anticalines" which are, among others, described in German patent application DE 197 42 706.

In a further aspect the present invention relates to functional nucleic acids interacting with any of the hyperimmune serum reactive antigens and fragments thereof according to the present invention, and a method for the manufacture of such functional nucleic acids whereby the method is characterized by the use of the hyperimmune serum reactive antigens and fragments thereof according to the present invention and the basic steps are known to the one skilled in the art. The functional nucleic acids are preferably aptamers and spiegelmers.

Aptamers are D-nucleic acids which are either single stranded or double stranded and which specifically interact with a target molecule. The manufacture or selection of aptamers is, e. g., described in European patent EP 0 533 838. Basically the following steps are realized. First, a mixture of nucleic acids, i. e. potential aptamers, is provided whereby each nucleic acid typically comprises a segment of several, preferably at least eight subsequent randomised nucleotides. This mixture is subsequently contacted with the target molecule whereby the nucleic acid(s) bind to the target molecule, such as based on an increased affinity towards the target or with a bigger force thereto, compared to the candidate mixture. The binding nucleic acid(s) are/is subsequently separated from the remainder of the mixture. Optionally, the thus obtained nucleic acid(s) is amplified using, e.g. polymerase chain reaction. These steps may be repeated several times giving at the end a mixture having an increased ratio of nucleic acids specifically binding to the target from which the final binding nucleic acid is then optionally selected. These specifically binding nucleic acid(s) are referred to aptamers. It is obvious that at any stage of the method for the generation or identification of the aptamers samples of the mixture of individual nucleic acids may be taken to determine the sequence thereof using standard techniques. It is within the present invention that the aptamers may be stabilized such as, e. g., by introducing defined chemical groups which are known to the one skilled in the art of generating aptamers. Such modification may for example reside in the

introduction of an amino group at the 2'-position of the sugar moiety of the nucleotides. Aptamers are currently used as therapeutical agens. However, it is also within the present invention that the thus selected or generated aptamers may be used for target validation and/or as lead substance for the development of medicaments, preferably of medicaments based on small molecules. This is actually done by a competition assay whereby the specific interaction between the target molecule and the aptamer is inhibited by a candidate drug whereby upon replacement of the aptamer from the complex of target and aptamer it may be assumed that the respective drug candidate allows a specific inhibition of the interaction between target and aptamer, and if the interaction is specific, said candidate drug will, at least in principle, be suitable to block the target and thus decrease its biological availability or activity in a respective system comprising such target. The thus obtained small molecule may then be subject to further derivatisation and modification to optimise its physical, chemical, biological and/or medical characteristics such as toxicity, specificity, biodegradability and bioavailability.

Spiegelmers and their generation or manufacture is based on a similar principle. The manufacture of spiegelmers is described in international patent application WO 98/08856. Spiegelmers are L-nucleic acids, which means that they are composed of L-nucleotides rather than D-nucleotides as aptamers are. Spiegelmers are characterized by the fact that they have a very high stability in biological system and, comparable to aptamers, specifically interact with the target molecule against which they are directed. In the process of generating spiegelmers, a heterogonous population of D-nucleic acids is created and this population is contacted with the optical antipode of the target molecule, in the present case for example with the D-enantiomer of the naturally occurring L-enantiomer of the hyperimmune serum reactive antigens and fragments thereof according to the present invention. Subsequently, those D-nucleic acids are separated which do not interact with the optical antipode of the target molecule. But those D-nucleic acids interacting with the optical antipode of the target molecule are separated, optionally determined and/or sequenced and subsequently the corresponding L-nucleic acids are synthesized based on the nucleic acid sequence information obtained from the D-nucleic acids. These L-nucleic acids which are identical in terms of sequence with the aforementioned D-nucleic acids interacting with the optical antipode of the target molecule, will specifically interact with the naturally occurring target molecule rather than with the optical antipode thereof. Similar to the method for the generation of aptamers it is also possible to repeat the various steps several times and thus to enrich those nucleic acids specifically interacting with the optical antipode of the target molecule.

In a further aspect the present invention relates to functional nucleic acids interacting with any of the nucleic acid molecules according to the present invention, and a method for the manufacture of such functional nucleic acids whereby the method is characterized by the use of the nucleic acid molecules and their respective sequences according to the present invention and the basic steps are known to the one skilled in the art. The functional nucleic acids are preferably ribozymes, antisense oligonucleotides and siRNA.

Ribozymes are catalytically active nucleic acids which preferably consist of RNA which basically comprises two moieties. The first moiety shows a catalytic activity whereas the second moiety is responsible for the specific interaction with the target nucleic acid, in the present case the nucleic acid coding for the hyperimmune serum reactive antigens and fragments thereof according to the present invention. Upon interaction between the target nucleic acid and the second moiety of the ribozyme, typically by hybridisation and Watson-Crick base pairing of essentially complementary stretches of bases on the two hybridising strands, the catalytically active moiety may become active which means that it catalyses, either intramolecularly or intermolecularly, the target nucleic acid in case the catalytic activity of the ribozyme is a phosphodiesterase activity. Subsequently, there may be a further degradation of the target nucleic acid which in the end results in the degradation of the target nucleic acid as well as the protein derived from the said target nucleic acid. Ribozymes, their use and design principles are known to the one skilled in the art, and, for example described in {Doherty, E. et al., 2001} and {Lewin, A. et al., 2001}.

The activity and design of antisense oligonucleotides for the manufacture of a medicament and as a diagnostic agent, respectively, is based on a similar mode of action. Basically, antisense oligonucleotides hybridise based on base complementarity, with a target RNA, preferably with a mRNA, thereby activate RNase H. RNase H is activated by both phosphodiester and phosphorothioate-coupled DNA. Phosphodiester-coupled DNA, however, is rapidly degraded by cellular nucleases with the exception of phosphorothioate-coupled DNA. These resistant, non-naturally occurring DNA derivatives do not inhibit RNase H upon hybridisation with RNA. In other words, antisense polynucleotides are only effective as DNA RNA hybride complexes. Examples for this kind of antisense oligonucleotides are described, among others, in US-patent US 5,849,902 and US 5,989,912. In other words, based on the nucleic acid sequence of the target molecule which in the present case are the nucleic acid molecules for the hyperimmune serum reactive antigens and fragments thereof according to the present invention, either from the target protein from which a respective nucleic acid sequence may in principle be deduced, or by knowing the nucleic acid sequence as such, particularly the mRNA, suitable antisense oligonucleotides may be designed base on the principle of base complementarity.

Particularly preferred are antisense-oligonucleotides which have a short stretch of phosphorothioate DNA (3 to 9 bases). A minimum of 3 DNA bases is required for activation of bacterial RNase H and a minimum of 5 bases is required for mammalian RNase H activation. In these chimeric oligonucleotides there is a central region that forms a substrate for RNase H that is flanked by hybridising "arms" comprised of modified nucleotides that do not form substrates for RNase H. The hybridising arms of the chimeric oligonucleotides may be modified such as by 2′-O-methyl or 2′-fluoro. Alternative approaches used methylphosphonate or phosphoramidate linkages in said arms. Further embodiments of the antisense oligonucleotide useful in the practice of the present invention are P-methoxyoligonucleotides, partial P-methoxyoligodeoxyribonucleotides or P-methoxyoligonucleotides.

Of particular relevance and usefulness for the present invention are those antisense oligonucleotides as more particularly described in the above two mentioned US patents. These oligonucleotides contain no naturally occurring 5′→3′-linked nucleotides. Rather the oligonucleotides have two types of nucleotides: 2′-deoxyphosphorothioate, which activate RNase H, and 2′-modified nucleotides, which do not. The linkages between the 2′-modified nucleotides can be phosphodiesters, phosphorothioate or P-ethoxyphosphodiester. Activation of RNase H is accomplished by a contiguous RNase H-activating region, which contains between 3 and 5 2′-deoxyphosphorothioate nucleotides to activate bacterial RNase H and between 5 and 10 2′- deoxyphosphorothioate nucleotides to activate eucaryotic and, particularly, mammalian RNase H. Protection from degradation is accomplished by making the 5′ and 3′ terminal bases highly nuclease resistant and, optionally, by placing a 3′ terminal blocking group.

More particularly, the antisense oligonucleotide comprises a 5′ terminus and a 3′ terminus; and from 11 to 59 5′→3′-linked nucleotides independently selected from the group consisting of 2′-modified phosphodiester nucleotides and 2′-modified P-alkyloxyphosphotriester nucleotides; and wherein the 5′-terminal nucleoside is attached to an RNase H-activating region of between three and ten contiguous phosphorothioate-linked deoxyribonucleotides, and wherein the 3′-terminus of said oligonucleotide is selected from the group consisting of an inverted deoxyribonucleotide, a contiguous stretch of one to three phosphorothioate 2′-modified ribonucleotides, a biotin group and a P-alkyloxyphosphotriester nucleotide.

Also an antisense oligonucleotide may be used wherein not the 5′ terminal nucleoside is attached to an RNase H-activating region but the 3′ terminal nucleoside as specified above. Also, the 5′ terminus is selected from the particular group rather than the 3′ terminus of said oligonucleotide.

The nucleic acids as well as the hyperimmune serum reactive antigens and fragments thereof according to the present invention may be used as or for the manufacture of pharmaceutical compositions,

especially vaccines. Preferably such pharmaceutical composition, preferably vaccine is for the prevention or treatment of diseases caused by, related to or associated with S. *pyogenes*. In so far another aspect of the invention relates to a method for inducing an immunological response in an individual, particularly a mammal, which comprises inoculating the individual with the hyperimmune serum reactive antigens and fragments thereof of the invention, or a fragment or variant thereof, adequate to produce antibodies to protect said individual from infection, particularly *Streptococcus* infection and most particularly *S. pyogenes* infections.

Yet another aspect of the invention relates to a method of inducing an immunological response in an individual which comprises, through gene therapy or otherwise, delivering a nucleic acid functionally encoding hyperimmune serum reactive antigens and fragments thereof, or a fragment or a variant thereof, for expressing the hyperimmune serum reactive antigens and fragments thereof, or a fragment or a variant thereof *in vivo* in order to induce an immunological response to produce antibodies or a cell mediated T cell response, either cytokine-producing T cells or cytotoxic T cells, to protect said individual from disease, whether that disease is already established within the individual or not. One way of administering the gene is by accelerating it into the desired cells as a coating on particles or otherwise.

A further aspect of the invention relates to an immunological composition which, when introduced into a host capable of having induced within it an immunological response, induces an immunological response in such host, wherein the composition comprises recombinant DNA which codes for and expresses an antigen of the hyperimmune serum reactive antigens and fragments thereof of the present invention. The immunological response may be used therapeutically or prophylactically and may take the form of antibody immunity or cellular immunity such as that arising from CTL or CD4+ T cells.

The hyperimmune serum reactive antigens and fragments thereof of the invention or a fragment thereof may be fused with a co-protein which may not by itself produce antibodies, but is capable of stabilizing the first protein and producing a fused protein which will have immunogenic and protective properties. This fused recombinant protein preferably further comprises an antigenic co-protein, such as Glutathione-S-transferase (GST) or beta-galactosidase, relatively large co-proteins which solubilise the protein and facilitate production and purification thereof. Moreover, the co-protein may act as an adjuvant in the sense of providing a generalized stimulation of the immune system. The co-protein may be attached to either the amino or carboxy terminus of the first protein.

Also, provided by this invention are methods using the described nucleic acid molecule or particular fragments thereof in such genetic immunization experiments in animal models of infection with *S. pyogenes*. Such fragments will be particularly useful for identifying protein epitopes able to provoke a prophylactic or therapeutic immune response. This approach can allow for the subsequent preparation of monoclonal antibodies of particular value from the requisite organ of the animal successfully resisting or clearing infection for the development of prophylactic agents or therapeutic treatments of *S. pyogenes* infection in mammals, particularly humans.

The hyperimmune serum reactive antigens and fragments thereof may be used as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria, for example by blocking adherence of bacteria to damaged tissue. Examples of tissue damage include wounds in skin or connective tissue caused e.g. by mechanical, chemical or thermal damage or by implantation of indwelling devices, or wounds in the mucous membranes, such as the mouth, mammary glands, urethra or vagina.

The present invention also includes a vaccine formulation which comprises the immunogenic recombinant protein together with a suitable carrier. Since the protein may be broken down in the stomach, it is preferably administered parenterally, including, for example, administration that is subcutaneous, intramuscular, intravenous, or intradermal. Formulations suitable for parenteral

administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the bodily fluid, preferably the blood, of the individual; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in-water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

According to another aspect, the present invention relates to a pharmaceutical composition comprising such a hyperimmune serum-reactive antigen or a fragment thereof as provided in the present invention for *S. pyogenes.* Such a pharmaceutical composition may comprise one or more hyperimmune serum reactive antigens or fragments thereof against *S. pyogenes.* Optionally, such *S. pyogenes* hyperimmune serum reactive antigens or fragments thereof may also be combined with antigens against other pathogens in a combination pharmaceutical composition. Preferably, said pharmaceutical composition is a vaccine for preventing or treating an infection caused by *S. pyogenes* and/or other pathogens against which the antigens have been included in the vaccine.

According to a further aspect, the present invention relates to a pharmaceutical composition comprising a nucleic acid molecule encoding a hyperimmune serum-reactive antigen or a fragment thereof as identified above for *S. pyogenes.* Such a pharmaceutical composition may comprise one or more nucleic acid molecules encoding hyperimmune serum reactive antigens or fragments thereof against *S. pyogenes.* Optionally, such *S. pyogenes* nucleic acid molecules encoding hyperimmune serum reactive antigens or fragments thereof may also be combined with nucleic acid molecules encoding antigens against other pathogens in a combination pharmaceutical composition. Preferably, said pharmaceutical composition is a vaccine for preventing or treating an infection caused by *S. pyogenes* and/or other pathogens against which the antigens have been included in the vaccine.

The pharmaceutical composition may contain any suitable auxiliary substances, such as buffer substances, stabilisers or further active ingredients, especially ingredients known in connection of pharmaceutical composition and/or vaccine production.

A preferable carrier/or excipient for the hyperimmune serum-reactive antigens, fragments thereof or a coding nucleic acid molecule thereof according to the present invention is an immunostimulatory compound for further stimulating the immune response to the given hyperimmune serum-reactive antigen, fragment thereof or a coding nucleic acid molecule thereof. Preferably the immunostimulatory compound in the pharmaceutical preparation according to the present invention is selected from the group of polycationic substances, especially polycationic peptides, immunostimulatory nucleic acids molecules, preferably immunostimulatory deoxynucleotides, alum, Freund's complete adjuvants, Freund's incomplete adjuvants, neuroactive compounds, especially human growth hormone, or combinations thereof.

It is also within the scope of the present invention that the pharmaceutical composition, especially vaccine, comprises apart from the hyperimmune serum reactive antigens, fragments thereof and/or coding nucleic acid molecules thereof according to the present invention other compounds which are biologically or pharmaceutically active. Preferably, the vaccine composition comprises at least one polycationic peptide. The polycationic compound(s) to be used according to the present invention may be any polycationic compound which shows the characteristic effects according to the WO 97/30721. Preferred polycationic compounds are selected from basic polyppetides, organic polycations, basic polyamino acids or mixtures thereof. These polyamino acids should have a chain length of at least 4 amino acid residues (WO 97/30721). Especially preferred are substances like polylysine, polyarginine and

polypeptides containing more than 20 %, especially more than 50 % of basic amino acids in a range of more than 8, especially more than 20, amino acid residues or mixtures thereof. Other preferred polycations and their pharmaceutical compositions are described in WO 97/30721 (e.g. polyethyleneimine) and WO 99/38528. Preferably these polypeptides contain between 20 and 500 amino acid residues, especially between 30 and 200 residues.

These polycationic compounds may be produced chemically or recombinantly or may be derived from natural sources.

Cationic (poly)peptides may also be anti-microbial with properties as reviewed in {Ganz, T., 1999}. These (poly)peptides may be of prokaryotic or animal or plant origin or may be produced chemically or recombinantly (WO 02/13857). Peptides may also belong to the class of defensins (WO 02/13857). Sequences of such peptides can be, for example, be found in the Antimicrobial Sequences Database under the following internet address:

http://www.bbcm.univ.trieste.it/~tossi/pag2.html

Such host defence peptides or defensives are also a preferred form of the polycationic polymer according to the present invention. Generally, a compound allowing as an end product activation (or down-regulation) of the adaptive immune system, preferably mediated by APCs (including dendritic cells) is used as polycationic polymer.

Especially preferred for use as polycationic substances in the present invention are cathelicidin derived antimicrobial peptides or derivatives thereof (International patent application WO 02/13857, incorporated herein by reference), especially antimicrobial peptides derived from mammal cathelicidin, preferably from human, bovine or mouse.

Polycationic compounds derived from natural sources include HIV-REV or HIV-TAT (derived cationic peptides, antennapedia peptides, chitosan or other derivatives of chitin) or other peptides derived from these peptides or proteins by biochemical or recombinant production. Other preferred polycationic compounds are cathelin or related or derived substances from cathelin. For example, mouse cathelin is a peptide which has the amino acid sequence NH_2-RLAGLLRKGGEKIGEKLKKIGOKIKNFFQKLVPQPE-COOH. Related or derived cathelin substances contain the whole or parts of the cathelin sequence with at least 15-20 amino acid residues. Derivations may include the substitution or modification of the natural amino acids by amino acids which are not among the 20 standard amino acids. Moreover, further cationic residues may be introduced into such cathelin molecules. These cathelin molecules are preferred to be combined with the antigen. These cathelin molecules surprisingly have turned out to be also effective as an adjuvant for a antigen without the addition of further adjuvants. It is therefore possible to use such cathelin molecules as efficient adjuvants in vaccine formulations with or without further immunactivating substances.

Another preferred polycationic substance to be used according to the present invention is a synthetic peptide containing at least 2 KLK-motifs separated by a linker of 3 to 7 hydrophobic amino acids (International patent application WO 02/32451, incorporated herein by reference).

The pharmaceutical composition of the present invention may further comprise immunostimulatory nucleic acid(s). Immunostimulatory nucleic acids are e. g. neutral or artificial CpG containing nucleic acid, short stretches of nucleic acid derived from non-vertebrates or in form of short oligonucleotides (ODNs) containing non-methylated cytosine-guanine di-nucleotides (CpG) in a certain base context (e.g. described in WO 96/02555). Alternatively, also nucleic acids based on inosine and cytidine as e.g. described in the WO 01/93903, or deoxynucleic acids containing deoxy-inosine and/or deoxyuridine residues (described in WO 01/93905 and PCT/EP 02/05448, incorporated herein by reference) may

preferably be used as immunostimulatory nucleic acids for the present invention. Preferablly, the mixtures of different immunostimulatory nucleic acids may be used according to the present invention.

It is also within the present invention that any of the aforementioned polycationic compounds is combined with any of the immunostimulatory nucleic acids as aforementioned. Preferably, such combinations are according to the ones as described in WO 01/93905, WO 02/32451, WO 01/54720, WO 01/93903, WO 02/13857 and PCT/EP 02/05448 and the Austrian patent application A 1924/2001, incorporated herein by reference.

In addition or alternatively such vaccine composition may comprise apart from the hyperimmune serum reactive antigens and fragments thereof, and the coding nucleic acid molecules thereof according to the present invention a neuroactive compound. Preferably, the neuroactive compound is human growth factor as, e.g. described in WO 01/24822. Also preferably, the neuroactive compound is combined with any of the polycationic compounds and/or immunostimulatory nucleic acids as afore-mentioned.

In a further aspect the present invention is related to a pharmaceutical composition. Such pharmaceutical composition is, for example, the vaccine described herein. Also a pharmaceutical composition is a pharmaceutical composition which comprises any of the following compounds or combinations thereof: the nucleic acid molecules according to the present invention, the hyperimmune serum reactive antigens and fragments thereof according to the present invention, the vector according to the present invention, the cells according to the present invention, the antibody according to the present invention, the functional nucleic acids according to the present invention and the binding peptides such as the anticalines according to the present invention, any agonists and antagonists screened as described herein. In connection therewith any of these compounds may be employed in combination with a non-sterile or sterile carrier or carriers for use with cells, tissues or organisms, such as a pharmaceutical carrier suitable for administration to a subject. Such compositions comprise, for instance, a media additive or a therapeutically effective amount of a hyperimmune serum reactive antigen and fragments thereof of the invention and a pharmaceutically acceptable carrier or excipient. Such carriers may include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol and combinations thereof. The formulation should suit the mode of administration.

The pharmaceutical compositions may be administered in any effective, convenient manner including, for instance, administration by topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal or intradermal routes among others.

In therapy or as a prophylactic, the active agent may be administered to an individual as an injectable composition, for example as a sterile aqueous dispersion, preferably isotonic.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1 % to about 98 % by weight of the formulation; more usually they will constitute up to about 80 % by weight of the formulation.

In addition to the therapy described above, the compositions of this invention may be used generally as a wound treatment agent to prevent adhesion of bacteria to matrix proteins exposed in wound tissue and for prophylactic use in dental treatment as an alternative to, or in conjunction with, antibiotic prophylaxis.

A vaccine composition is conveniently in injectable form. Conventional adjuvants may be employed to enhance the immune response. A suitable unit dose for vaccination is 0.05-5 μg/kg of antigen, and such dose is preferably administered 1-3 times and with an interval of 1-3 weeks.

With the indicated dose range, no adverse toxicological effects should be observed with the compounds of the invention which would preclude their administration to suitable individuals.

In a further embodiment the present invention relates to diagnostic and pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention. The ingredient(s) can be present in a useful amount, dosage, formulation or combination. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, reflecting approval by the agency of the manufacture, use or sale of the product for human administration.

In connection with the present invention any disease related use as disclosed herein such as, e. g. use of the pharmaceutical composition or vaccine, is particularly a disease or diseased condition which is caused by, linked or associated with Streptococci, more preferably, *S. pyogenes*. In connection therewith it is to be noted that *S. pyogenes* comprises several strains including those disclosed herein. A disease related, caused or associated with the bacterial infection to be prevented and/or treated according to the present invention includes besides others bacterial pharyngitis, scarlet fever, impetigo, rheumatic fever, necrotizing fasciitis and sepsis in humans.

In a still further embodiment the present invention is related to a screening method using any of the hyperimmune serum reactive antigens or nucleic acids according to the present invention. Screening methods as such are known to the one skilled in the art and can be designed such that an agonist or an antagonist is screened. Preferably an antagonist is screened which in the present case inhibits or prevents the binding of any hyperimmune serum reactive antigen and fragment thereof according to the present invention to an interaction partner. Such interaction partner can be a naturally occurring interaction partner or a non-naturally occurring interaction partner.

The invention also provides a method of screening compounds to identify those which enhance (agonist) or block (antagonist) the function of hyperimmune serum reactive antigens and fragments thereof or nucleic acid molecules of the present invention, such as its interaction with a binding molecule. The method of screening may involve high-throughput.

For example, to screen for agonists or antagonists, the interaction partner of the nucleic acid molecule and nucleic acid, respectively, according to the present invention, maybe a synthetic reaction mix, a cellular compartment, such as a membrane, cell envelope or cell wall, or a preparation of any thereof, may be prepared from a cell that expresses a molecule that binds to the hyperimmune serum reactive antigens and fragments thereof of the present invention. The preparation is incubated with labelled hyperimmune serum reactive antigens and fragments thereof in the absence or the presence of a candidate molecule which may be an agonist or antagonist. The ability of the candidate molecule to bind the binding molecule is reflected in decreased binding of the labelled ligand. Molecules which bind gratuitously, i. e., without inducing the functional effects of the hyperimmune serum reactive antigens and fragments thereof, are most likely to be good antagonists. Molecules that bind well and elicit functional effects that are the same as or closely related to the hyperimmune serum reactive antigens and fragments thereof are good agonists.

The functional effects of potential agonists and antagonists may be measured, for instance, by determining the activity of a reporter system following interaction of the candidate molecule with a cell or appropriate cell preparation, and comparing the effect with that of the hyperimmune serum reactive

antigens and fragments thereof of the present invention or molecules that elicit the same effects as the hyperimmune serum reactive antigens and fragments thereof. Reporter systems that may be useful in the regard include but are not limited to colorimetric labelled substrate converted into product, a reporter gene that is responsive to changes in the functional activity of the hyperimmune serum reactive antigens and fragments thereof, and binding assays known in the art.

Another example of an assay for antagonists is a competitive assay that combines the hyperimmune serum reactive antigens and fragments thereof of the present invention and a potential antagonist with membrane-bound binding molecules, recombinant binding molecules, natural substrates or ligands, or substrate or ligand mimetics, under appropriate conditions for a competitive inhibition assay. The hyperimmune serum reactive antigens and fragments thereof can be labelled such as by radioactivity or a colorimetric compound, such that the molecule number of hyperimmune serum reactive antigens and fragments thereof bound to a binding molecule or converted to product can be determined accurately to assess the effectiveness of the potential antagonist.

Potential antagonists include small organic molecules, peptides, polypeptides and antibodies that bind to a hyperimmune serum reactive antigen and fragments thereof of the invention and thereby inhibit or extinguish its acitivity. Potential antagonists also may be small organic molecules, a peptide, a polypeptide such as a closely related protein or antibody that binds to the same sites on a binding molecule without inducing functional activity of the hyperimmune serum reactive antigens and fragments thereof of the invention.

Potential antagonists include a small molecule which binds to and occupies the binding site of the hyperimmune serum reactive antigens and fragments thereof thereby preventing binding to cellular binding molecules, such that normal biological activity is prevented. Examples of small molecules include but are not limited to small organic molecules, peptides or peptide-like molecules. Other potential antagonists include antisense molecules.

Other potential antagonists include antisense molecules (see {Okano, H. et al., 1991}; OLIGODEOXYNUCLEOTIDES AS ANTISENSE INHIBITORS OF GENE EXPRESSION; CRC Press, Boca Ration, FL (1988), for a description of these molecules).

Preferred potential antagonists include derivatives of the hyperimmune serum reactive antigens and fragments thereof of the invention.

As used herein the activity of a hyperimmune serum reactive antigen and fragment thereof according to the present invention is its capability to bind to any of its interaction partner or the extent of such capability to bind to its or any interaction partner.

In a particular aspect, the invention provides the use of the hyperimmune serum reactive antigens and fragments thereof, nucleic acid molecules or inhibitors of the invention to interfere with the initial physical interaction between a pathogen and mammalian host responsible for sequelae of infection. In particular the molecules of the invention may be used: i) in the prevention of adhesion of *S. pyogenes* to mammalian extracellular matrix proteins on in-dwelling devices or to extracellular matrix proteins in wounds; ii) to block protein mediated mammalian cell invasion by, for example, initiating phosphorylation of mammalian tyrosine kinases. {Rosenshine, I. et al., 1992}to block bacterial adhesion between mammalian extracellular matrix proteins and bacterial proteins which mediate tissue damage; iv) to block the normal progression of pathogenesis in infections initiated other than by the implantation of in-dwelling devices or by other surgical techniques.

Each of the DNA coding sequences provided herein may be used in the discovery and development of

antibacterial compounds. The encoded protein upon expression can be used as a target for the screening of antibacterial drugs. Additionally, the DNA sequences encoding the amino terminal regions of the encoded protein or Shine-Delgarno or other translation facilitating sequences of the respective mRNA can be used to construct antisense sequences to control the expression of the coding sequence of interest.

The antagonists and agonists may be employed, for instance, to inhibit diseases arising from infection with Streptococcus, especially *S. pyogenes*, such as sepsis.

In a still further aspect the present invention is related to an affinity device such affinity device comprises as least a support material and any of the hyperimmune serum reactive antigens and fragments thereof according to the present invention which is attached to the support material. Because of the specificity of the hyperimmune serum reactive antigens and fragments thereof according to the present invention for their target cells or target molecules or their interaction partners, the hyperimmune serum reactive antigens and fragments thereof allow a selective removal of their interaction partner(s) from any kind of sample applied to the support material provided that the conditions for binding are met. The sample may be a biological or medical sample, including but not limited to, fermentation broth, cell debris, cell preparation, tissue preparation, organ preparation, blood, urine, lymph liquid, liquor and the like.

The hyperimmune serum reactive antigens and fragments thereof may be attached to the matrix in a covalent or non-covalent manner. Suitable support material is known to the one skilled in the art and can be selected from the group comprising cellulose, silicon, glass, aluminium, paramagnetic beads, starch and dextrane.

The present invention is further illustrated by the following figures, examples and the sequence listing from which further features, embodiments and advantages may be taken. It is to be understood that the present examples are given by way of illustration only and not by way of limitation of the disclosure.

In connection with the present invention

Figure 1 shows the characterization of *S. pyogenes* specific human sera.

Figure 2 shows the characterization of the small fragment genomic library, LSPy-70, from *Streptococcus pyogenes* SF370/M1.

Figure 3 shows the selection of bacterial cells by MACS using biotinylated human IgGs.

Figure 4 shows an example for the gene distribution study with the identified antigens.

Figure 5 shows cell surface staining by flow cytometry.

Figure 6 shows the protective value of identified recombinant S. pyogenes antigens.

Table 1 shows the summary of all screens performed with genomic *S. pyogenes* libraries and human serum.

Table 2 shows the epitope serology with human sera.

Table 3 shows the summary of the gene distribution analysis for the identified antigens in fifty *S. pyogenes* strains.

Table 4 summarizes the information on the antigenic proteins used for the immunization experiments.

Table 5 shows the variability of antigenic proteins in six different strains of S. pyogenes.

The figures to which it might be referred to in the specification are described in the following in more details.

Figure 1 shows the characterization of human sera for *S. pyogenes* as measured by ELISA.

Figure 2 shows the fragment size distribution of the *Streptococcus pyogenes* SF370/M1 small fragment genomic library, LSPy-70. After sequencing 576 randomly selected clones sequences were trimmed to eliminate vector residues and the number of clones with various genomic fragment sizes were plotted. (B) Graphic illustration of the distribution of the same set of randomly sequenced clones of LSPy-70 over the *S. pyogenes* chromosome. Blue circles indicate matching sequences to annotated ORFs in +/+ orientation. Red rectangles represent fully matched clones to non-coding chromosomal sequences in +/+ orientation. Green diamonds positions all clones with complementary or chimeric sequences. Numeric distances in base pairs are indicated over each circular genome for orientation. Partitioning of various clone sets within the library is given in numbers and percentage at the bottom of the figure.

Figure 3A shows the MACS selection with biotinylated human IgGs. The LSPy-70 library in pMAL9.1 was screened with 10 μg biotinylated, human serum (P4-IgG) in the first and with 1 μg in the second selection round. As negative control, no serum was added to the library cells for screening. Number of cells selected after the 1st and 2nd elution are shown for each selection round. Figure 3B shows the reactivity of specific clones (1-52) isolated by bacterial surface display as analysed by Western blot analysis with the human serum (P4-IgG) used for selection by MACS at a dilution of 1:3,000. As a loading control the same blot was also analysed with antibodies directed against the platform protein LamB at a dilution of 1:5,000. LB, Extract from a clone expressing LamB without foreign peptide insert.

Figure 4A shows the emm types of *S. pyogenes* analysed for the gene distribution study. Figure 4B shows the PCR analysis for the gene distribution of genes Spy0269 with the respective oligonucleotides. The predicted size of the PCR fragments is 1,000 bp. 1-50, *S. pyogenes* strains as listed under A; N, no genomic DNA added; P, genomic DNA from *S. pyogenes* SF310, which served as template for library construction.

Figure 5 Detection of specific antibody binding on the cell surface of Group A Streptococcus by flow cytometry. In Figure 5A preimmune mouse sera and polyclonal sera raised against *S.pyogenes* lysate were incubated with *S. pyogenes* strain SF370/M1 and analysed by flow cytometry. Control represents the level of non-specific binding of the secondary antibody to the surface of *S.pyogenes* cells. The histograms in figure 5B and 5C indicate the increased fluorescence due to specific binding of anti-Spy0012 (B) or anti-Spy1315 and anti-Spy1798 (C) antibodies in comparison to the control sera against the two platform proteins LamB and FhuA, respectively.

Figure 6 NMRI mice were immunized with 3 consecutive doses of recombinant protein (50μg/dose) two weeks apart on days 0, 14 and 28. As negative control, mice were immunized with PBS in the presence of adjuvant. The M1 protein (Spy2018) served as positive control for the challenge experiment. The bacterial challenge was performed with 5x10^7 *S. pyogenes* AP1 cells i.v. and survival of mice was observed daily for **A)** 18 days, **B)** 21 days and **C)** 19 days, respectively.

Table 1: Immunogenic proteins identified by bacterial surface display.

A, LSPy-70 library in lamB with IC3-IgG (1588), B, LSPy-70 library in lamB with IC3-IgA (1539), C, LSPy-70 library in lamB with IC6-IgG (1173), D, LSPy-70 library in lamB with P4-IgG (1138), E, LSPy-70 library in lamB with P4-IgA (981), F, LSPy-150 library in btuB with IC3-IgG (991), G, LSPy-150 library in btuB with IC6-IgG (1036), H, LSPy-150 library in btuB with P4-IgG (681), I, LSPy-400 library in fhuA with IC3-

IgG (559), K, LSPy-400 library in fhuA with IC6-IgG (543), L, LSPy-400 library in fhuA with P4-IgG (20), *, prediction of antigenic sequences longer than 5 amino acids was performed with the program ANTIGENIC {Kolaskar, A. et al., 1990}.

Table 2: Epitope serology with human sera.
Immune reactivity of individual synthetic peptides representing selected epitopes with individual human sera is shown. Extent of reactivity is pattern/grey coded; white: - (<50U), grey: + (50-119U), diagonal: ++ (120-199U), diagonally crossed: +++ (200-1000U) and vertically crossed: ++++ (> 1000U). ELISA units (U) are calculated from OD_{545nm} readings and the serum dilution after correction for background. Score, sum of all reactivities (addition of the number of all +); P1 to P10 sera are from patients with acute pharyngitis and N1 to N10 sera are from healthy adults. P and N are used as internal controls.
Peptide names: SPO0012, annotated ORF Spy0012; SPA0450, potential novel ORF in alternative reading-frame of Spy0450; SPC0406, potential novel ORF on complement of Spy0406; SPN0001, potential novel ORF in non-coding region.

Table 3: Gene distribution in *S. pyogenes* strains.
Fifty *S. pyogenes* strains as shown in Figure 4A were tested by PCR with oligonucleotides specific for the genes encoding relevant antigens. The PCR fragment of one selected PCR fragment was sequenced in order to confirm the amplification of the correct DNA fragment. *, number of amino acid substitutions in strain M89 as compared to *S. pyogenes* SF370 (M1). #, alternative strain used for sequencing, because gene was not present in M89.

Table 4: Recombinant proteins used for immunisation experiments in NMRI mice.
Immunization with recombinant antigens and challenge with pathogenic *S. pyogenes* AP1 was performed as described under Experimental procedures. **A,** The amino acids of the respective antigen contained within the recombinant protein as used for the immunization experiments in animals are given in relation to the full-length protein. **B,** Percentage of survival is represented as protection and parentheses describes the percentage of protection of the negative control (PBS immunized) followed by the percentage of protection of the positive control (Spy2018). **C,** Spy0269 was selected due to the fact that the mice showed better survival although at the end of the observation time all mice died. This is reflected by the average survival time as measured in days: 14.6 (Spy0269), 11.6 (PBS) and 19.3 days (Spy2018).

Table 5: Sequence variation of antigenic proteins from *S. pyogenes*.
Antigenic proteins were analysed for amino acid exchanges in six different *S. pyogenes* strains as listed under experimental procedures. The residue number indicates the position of the amino acid in the full-length protein. In case of Spy1666, changes relative to a homologous gene in *Streptococcus pneumoniae* TIGR4 (SP0334) are listed, because the gene is highly conserved in *S. pyogenes* as well as *S. pneumoniae*. **A,** amino acid residue in protein from *S. pyogenes* SF370. **B,** amino acid residue(s), which may occur in any one the analysed genes from the other five *S. pyogenes* strains, if different from *S. pyogenes* SF370. **C,** residues of Spy0416 involved in catalytic activity. Changes in these residues are anticipated to render the enzyme inactive and are therefore exchanged experimentally with alanine, serine, threonine of glycine to produce an enzymatically inactive recombinant protein.

EXAMPLES

Example 1: Preparation of antibodies from human serum

The antibodies produced against group A streptococci by the human immune system and present in human sera are indicative of the in vivo expression of the antigenic proteins and their immunogenicity. These molecules are essential for the identification of individual antigens in the approach as described in the present invention, which is based on the interaction of the specific anti-streptococcal antibodies and

the corresponding *S. pyogenes* peptides or proteins. To gain access to relevant antibody repertoires, human sera were collected from

I. patients with acute *S. pyogenes* infections, such as pharyngitis, wound infection and bacteraemia. (*S. pyogenes* was shown to be the causative agent by medical microbiological tests),

II. uninfected healthy adults, since group A streptococcal infections are common, and antibodies are present as a consequence of natural immunization from previous encounters with streptococci.

The sera were characterized for anti-*S. pyogenes* antibodies by a series of ELISA and immunoblotting assays. Several streptococcal antigens have been used to show that the titers measured were not a result of the sum of cross-reactive antibodies. For that purpose two different antigen preparation were used: whole cell extract or culture supernatant proteins prepared from *S. pyogenes* SF370/M1 cultured overnight (stationary phase) in THB (Todd-Hewitt Broth) growth medium. Both IgG and IgA antibody levels were determined. Sera were selected for further analysis by immunoblotting based on total antibody titers against the two antigen preparations.

The titers were compared at given dilutions where the response was linear (Figure 1). Sera were ranked based on the reactivity against multiple streptococcal components, and the highest ones were selected for further analysis by immunoblotting. This extensive antibody characterization approach has led to the unambiguous identification of anti-streptococcal hyperimmune sera.

Recently it was reported that not only IgG, but also IgA serum antibodies can be recognized by the FcRIII receptors of PMNs and promote opsonization {Phillips-Quagliata, J. et al., 2000; Shibuya, A. et al., 2000}. The primary role of IgA antibodies is neutralization, mainly at the mucosal surface. The level of serum IgA reflects the quality, quantity and specificity of the dimeric secretory IgA. For that reason the serum collection was not only analyzed for anti-streptococcal IgG, but also for IgA levels. In the ELISA assays highly specific secondary reagents were used to detect antibodies from the high affinity types, such as IgG and IgA, but avoided IgM. Production of IgM antibodies occurs during the primary adaptive humoral response, and results in low affinity antibodies, while IgG and IgA antibodies had already undergone affinity maturation, and are more valuable in fighting or preventing disease

Experimental procedures

Peptide synthesis

Peptides were synthesized in small scale (4 mg resin; up to 288 in parallel) using standard F-moc chemistry on a Rink amide resin (PepChem, Tübingen, Germany) using a SyroII synthesizer (Multisyntech, Witten, Germany). After the sequence was assembled, peptides were elongated with Fmoc-epsilon-aminohexanoic acid (as a linker) and biotin (Sigma, St. Louis, MO; activated like a normal amino acid). Peptides were cleaved off the resin with 93%TFA, 5% triethylsilane, and 2% water for one hour. Peptides were dried under vacuum and freeze dried three times from acetonitrile/water (1:1). The presence of the correct mass was verified by mass spectrometry on a Reflex III MALDI-TOF (Bruker, Bremen Germany). The peptides were used without further purification.

Enzyme linked immune assay (ELISA).

For serum characterization: ELISA plates (Maxisorb, Millipore) were coated with 5-10 µg/ml total protein diluted in coating buffer (0.1M sodium carbonate pH 9.2). Three dilutions of sera (2,000X, 10,000X, 50,000X) were made in PBS-BSA.

For peptide serology: Biotin-labeled peptides were coating on Streptavidin ELISA plates (EXICON) at 10 µg/ml concentration according to the manufacturer's instructions. Sera were tested at two dilutions, 200X and 1,000X.

Highly specific Horse Radish Peroxidase (HRP)-conjugated anti-human IgG or anti-human IgA secondary antibodies (Southern Biotech) were used according to the manufacturers' recommendations (dilution: 1,000x). Antigen-antibody complexes were quantified by measuring the conversion of the substrate (ABTS) to colored product based on OD_{405nm} readings in an automated ELISA reader (TECAN

SUNRISE). Following manual coating, peptide plates were processed and analyzed by the Gemini 160 ELISA robot (TECAN) with a built-in reader (GENIOS, TECAN).

Immunoblotting
Total bacterial lysate and culture supernatant samples were prepared from *in vitro* grown *S. pyogenes* SF370/M1. 10 to 25μg total protein/lane was separated by SDS-PAGE using the BioRad Mini-Protean 3 Cell electrophoresis system and proteins transferred to nitrocellulose membrane (ECL, Amersham Pharmacia). After overnight blocking in 5% milk, antisera at 2,000x dilution were added, and HRPO labeled anti-mouse IgG was used for detection.

Preparation of bacterial antigen extracts
Total bacterial lysate: Bacteria were lysed by repeated freeze-thaw cycles: incubation on dry ice/ethanol-mixture until frozen (1 min), then thawed at 37°C (5 min): repeated 3 times. This was followed by sonication and collection of supernatant by centrifugation (3,500 rpm, 15 min, 4°C).
Culture supernatant: After removal of bacteria, the supernatant of overnight grown bacterial cultures was precipitated with ice-cold ethanol (100%): 1 part supernatant/3 parts ethanol incubated o/n at -20°C. Precipitates were collected by centrifugation (2,600 g, for 15 min) and dried. Dry pellets were dissolved either in PBS for ELISA, or in urea and SDS-sample buffer for SDS-PAGE and immunoblotting. The protein concentration of samples was determined by Bradford assay.

Purification of antibodies for genomic screening. Five sera from both the patient and the non-infected group were selected based on the overall anti-streptococcal titers for a serum pool used in the screening procedure. Antibodies against *E. coli* proteins were removed by incubating the heat-inactivated sera with whole cell *E. coli* cells (DH5alpha, transformed with pHIE11, grown under the same condition as used for bacterial surface display). Highly enriched preparations of IgGs from the pooled, depleted sera were generated by protein G affinity chromatography, according to the manufacturer's instructions (UltraLink Immobilized Protein G, Pierce). IgA antibodies were purified also by affinity chromatography using biotin-labeled anti-human IgA (Southern Biotech) immobilized on Streptavidin-agarose (GIBCO BRL). The efficiency of depletion and purification was checked by SDS-PAGE, Western blotting, ELISA and protein concentration measurements.

Example 2: Generation of highly random, frame-selected, small-fragment, genomic DNA libraries of *Streptococcus pyogenes*

Experimental procedures
Preparation of streptococcal genomic DNA. 50 ml Todd-Hewitt Broth medium was inoculated with *S. pyogenes* SF370/M1 bacteria from a frozen stab and grown with aeration and shaking for 18 h at 37°C. The culture was then harvested, centrifuged with 1,600x g for 15 min and the supernatant was removed. Bacterial pellets were washed 3 x with PBS and carefully re-suspended in 0.5 ml of Lysozyme solution (100 mg/ml). 0.1 ml of 10 mg/ml heat treated RNase A and 20 U of RNase T1 were added, mixed carefully and the solution was incubated for 1 h at 37°C. Following the addition of 0.2 ml of 20 % SDS solution and 0.1 ml of Proteinase K (10 mg/ml) the tube was incubated overnight at 55 °C. 1/3 volume of saturated NaCl was then added and the solution was incubated for 20 min at 4°C. The extract was pelleted in a microfuge (13,000 rpm) and the supernatant transferred into a new tube. The solution was extracted with $PhOH/CHCl_3/IAA$ (25:24:1) and with $CHCl_3/IAA$ (24:1). DNA was precipitated at room temperature by adding 0.6x volume of Isopropanol, spooled from the solution with a sterile Pasteur pipette and transferred into tubes containing 80% ice-cold ethanol. DNA was recovered by centrifuging the precipitates with 10-12,000x g, then dried on air and dissolved in ddH_2O.

Preparation of small genomic DNA fragments. Genomic DNA fragments were mechanically sheared into fragments ranging in size between 150 and 300 bp using a cup-horn sonicator (Bandelin Sonoplus UV

2200 sonicator equipped with a BB5 cup horn, 10 sec. pulses at 100 % power output) or into fragments of size between 50 and 70 bp by mild DNase I treatment (Novagen). It was observed that sonication yielded a much tighter fragment size distribution when breaking the DNA into fragments of the 150-300 bp size range. However, despite extensive exposure of the DNA to ultrasonic wave-induced hydromechanical shearing force, subsequent decrease in fragment size could not be efficiently and reproducibly achieved. Therefore, fragments of 50 to 70 bp in size were obtained by mild DNase I treatment using Novagen's shotgun cleavage kit. A 1:20 dilution of DNase I provided with the kit was prepared and the digestion was performed in the presence of $MnCl_2$ in a 60 μl volume at 20°C for 5 min to ensure double-stranded cleavage by the enzyme. Reactions were stopped with 2 μl of 0.5 M EDTA and the fragmentation efficiency was evaluated on a 2% TAE-agarose gel. This treatment resulted in total fragmentation of genomic DNA into near 50-70 bp fragments. Fragments were then blunt-ended twice using T4 DNA Polymerase in the presence of 100 μM each of dNTPs to ensure efficient flushing of the ends. Fragments were used immediately in ligation reactions or frozen at -20°C for subsequent use.

Description of the vectors. The vector pMAL4.31 was constructed on a pASK-IBA backbone {Skerra, A., 1994} with the beta-lactamase (*bla*) gene exchanged with the Kanamycin resistance gene. In addition *bla* gene was cloned into the multiple cloning site. The sequence encoding mature beta-lactamase is preceded by the leader peptide sequence of *ompA* to allow efficient secretion across the cytoplasmic membrane. Furthermore a sequence encoding the first 12 amino acids (spacer sequence) of mature beta-lactamase follows the *ompA* leader peptide sequence to avoid fusion of sequences immediately after the leader peptidase cleavage site, since e.g. clusters of positive charged amino acids in this region would decrease or abolish translocation across the cytoplasmic membrane {Kajava, A. et al., 2000}. A *Sma*I restriction site serves for library insertion. An upstream FseI site and a downstream NotI site, which were used for recovery of the selected fragment, flank the *Sma*I site. The three restriction sites are inserted after the sequence encoding the 12 amino acid spacer sequence in such a way that the *bla* gene is transcribed in the -1 reading frame resulting in a stop codon 15 bp after the *Not*I site. A +1 bp insertion restores the *bla* ORF so that beta-lactamase protein is produced with a consequent gain of Ampicillin resistance.

The vector pMAL9.1 was constructed by cloning the *lamB* gene into the multiple cloning site of pEH1 {Hashemzadeh-Bonehi, L. et al., 1998}. Subsequently, a sequence was inserted in *lamB* after amino acid 154, containing the restriction sites *Fse*I, *Sma*I and *Not*I. The reading frame for this insertion was constructed in such a way that transfer of frame-selected DNA fragments excised by digestion with *Fse*I and *Not*I from plasmid pMAL4.31 yields a continuous reading frame of *lamB* and the respective insert.

The vector pMAL10.1 was constructed by cloning the *btuB* gene into the multiple cloning site of pEH1. Subsequently, a sequence was inserted in *btuB* after amino acid 236, containing the restriction sites *Fse*I, *Xba*I and *Not*I. The reading frame for this insertion was chosen in a way that transfer of frame-selected DNA fragments excised by digestion with *Fse*I and *Not*I from plasmid pMAL4.31 yields a continuous reading frame of *btuB* and the respective insert.

The vector pHIE11 was constructed by cloning the *fhuA* gene into the multiple cloning site of pEH1. Thereafter, a sequence was inserted in *fhuA* after amino acid 405, containing the restriction site *Fse*I, *Xba*I and *Not*I. The reading frame for this insertion was chosen in a way that transfer of frame-selected DNA fragments excised by digestion with *Fse*I and *Not*I from plasmid pMAL4.31 yields a continuous reading frame of *fhuA* and the respective insert.

Cloning and evaluation of the library for frame selection. Genomic *S. pyogenes* DNA fragments were ligated into the *Sma*I site of the vector pMAL4.31. Recombinant DNA was electroporated into DH10B electrocompetent *E. coli* cells (GIBCO BRL) and transformants plated on LB-agar supplemented with Kanamycin (50 μg/ml) and Ampicillin (50 μg/ml). Plates were incubated over night at 37°C and colonies collected for large scale DNA extraction. A representative plate was stored and saved for collecting colonies for colony PCR analysis and large-scale sequencing. A simple colony PCR assay was used to

initially determine the rough fragment size distribution as well as insertion efficiency. From sequencing data the precise fragment size was evaluated, junction intactness at the insertion site as well as the frame selection accuracy (*3n+1 rule*).

Cloning and evaluation of the library for bacterial surface display. Genomic DNA fragments were excised from the pMAL4.31 vector, containing the *S. pyogenes* library with the restriction enzymes *Fse*I and *Not*I. The entire population of fragments was then transferred into plasmids pMAL9.1 (LamB), pMAL10.1 (BtuB) or pHIE11 (FhuA), which have been digested with *Fse*I and *Not*I. Using these two restriction enzymes, which recognise an 8 bp GC rich sequence, the reading frame that was selected in the pMAL4.31 vector is maintained in each of the platform vectors. The plasmid library was then transformed into *E. coli* DH5alpha cells by electroporation. Cells were plated onto large LB-agar plates supplemented with 50 µg/ml Kanamycin and grown over night at 37°C at a density yielding clearly visible single colonies. Cells were then scraped off the surface of these plates, washed with fresh LB medium and stored in aliquots for library screening at -80°C.

Results

Libraries for frame selection. Three libraries (LSPy70, LSPy150 and LSPy300) were generated in the pMAL4.31 vector with sizes of approximately 70, 150 and 300 bp, respectively. For each library, ligation and subsequent transformation of approximately 1 µg of pMAL4.31 plasmid DNA and 50 ng of fragmented genomic *S. pyogenes* DNA yielded 4x 10^5 to 2x 10^6 clones after frame selection. To assess the randomness of the libraries, approximately 600 randomly chosen clones of LSPy70 were sequenced. The bioinformatic analysis showed that of these clones only very few were present more than once. Furthermore, it was shown that 90% of the clones fell in the size range between 16 and 61 bp with an average size of 34 bp (Figure 2). All sequences followed the 3n+1 rule, showing that all clones were properly frame selected.

Bacterial surface display libraries. The display of peptides on the surface of *E. coli* required the transfer of the inserts from the LSPy libraries from the frame selection vector pMAL4.31 to the display plasmids pMAL9.1 (LamB), pMAL10.1 (BtuB) or pHIE11 (FhuA). Genomic DNA fragments were excised by *Fse*I and *Not*I restriction and ligation of 5ng inserts with 0.1µg plasmid DNA and subsequent transformation into DH5alpha cells resulted in 2-5x 10^6 clones. The clones were scraped off the LB plates and frozen without further amplification.

Example 3: Identification of highly immunogenic peptide sequences from *S. pyogenes* using bacterial surface displayed genomic libraries and human serum

Experimental procedures

MACS screening. Approximately 2.5x 10^8 cells from a given library were grown in 5 ml LB-medium supplemented with 50 µg/ml Kanamycin for 2 h at 37°C. Expression was induced by the addition of 1 mM IPTG for 30 min. Cells were washed twice with fresh LB medium and approximately 2x 10^7 cells re-suspended in 100 µl LB medium and transferred to an Eppendorf tube.

10 µg of biotinylated, human IgGs from purified from serum was added to the cells and the suspension incubated over night at 4°C with gentle shaking. 900 µl of LB medium was added, the suspension mixed and subsequently centrifuged for 10 min at 6,000 rpm at 4°C (For IgA screens, 10 µg of purified IgAs were used and these captured with biotinylated anti-human-IgG secondary antibodies). Cells were washed once with 1 ml LB and then re-suspended in 100 µl LB medium. 10 µl of MACS microbeads coupled to streptavidin (Miltenyi Biotech, Germany) were added and the incubation continued for 20 min at 4°C. Thereafter 900 µl of LB medium was added and the MACS microbead cell suspension was loaded onto the equilibrated MS column (Miltenyi Biotech, Germany) which was fixed to the magnet. (The MS

columns were equilibrated by washing once with 1 ml 70% EtOH and twice with 2 ml LB medium.)

The column was then washed three times with 3 ml LB medium. After removal of the magnet, cells were eluted by washing with 2 ml LB medium. After washing the column with 3 ml LB medium, the 2 ml eluate was loaded a second time on the same column and the washing and elution process repeated. The loading, washing and elution process was performed a third time, resulting in a final eluate of 2 ml.

A second round of screening was performed as follows. The cells from the final eluate were collected by centrifugation and re-suspended in 1 ml LB medium supplemented with 50 μg/ml Kanamycin. The culture was incubated at 37°C for 90 min and then induced with 1 mM IPTG for 30 min. Cells were subsequently collected, washed once with 1 ml LB medium and suspended in 10 μl LB medium. Since the volume was reduced, 1 μg of human, biotinylated IgGs was added and the suspension incubated over night at 4°C with gentle shaking. All further steps were exactly the same as in the first selection round. Cells selected after two rounds of selection were plated onto LB-agar plates supplemented with 50 μg/ml Kanamycin and grown over night at 37°C.

Evaluation of selected clones by sequencing and Western blot analysis. Selected clones were grown over night at 37°C in 3 ml LB medium supplemented with 50 μg/ml Kanamycin to prepare plasmid DNA using standard procedures. Sequencing was performed at MWG (Germany) or in collaboration with TIGR (U.S.A.).

For Western blot analysis approximately 10 to 20 μg of total cellular protein was separated by 10% SDS-PAGE and blotted onto HybondC membrane (Amersham Pharmacia Biotech, England). The LamB, BtuB or FhuA fusion proteins were detected using human serum as the primary antibody at a dilution of approximately 1:5,000 and anti-human IgG or IgA antibodies coupled to HRP at a dilution of 1:5,000 as secondary antibodies. Detection was performed using the ECL detection kit (Amersham Pharmacia Biotech, England). Alternatively, rabbit anti FhuA or mouse anti LamB antibodies were used as primary antibodies in combination with the respective secondary antibodies coupled to HRP for the detection of the fusion proteins.

Results

Screening of bacterial surface display libraries by magnetic activated cell sorting (MACS) using biotinylated Igs. The libraries LSPy70 in pMAL9.1, LSPy150 in pMAL10.1 and LSPy300 in pHIE11 were screened with pools of biotinylated, human IgGs and IgAs from patient sera or sera from healthy individuals (see Example 1: *Preparation of antibodies from human serum*). The selection procedure was performed as described under Experimental procedures. Figure 3A shows a representative example of a screen with the LSPy-70 library and P4-IgGs. As can be seen from the colony count after the first selection cycle from MACS screening, the total number of cells recovered at the end is drastically reduced from 3x 10^7 cells to approximately 5x 10^4 cells, whereas the selection without antibodies added showed a reduction to about 2x10^3 cells (Figure 3A). After the second round, a similar number of cells was recovered with P4-IgG, while fewer than 10 cells were recovered when no IgGs from human serum were added, clearly showing that selection was dependent on *S. pyogenes* specific antibodies. To evaluate the performance of the screen, approximately 50 selected clones were picked randomly and subjected to Western blot analysis with the same, pooled serum (Figure 3B). This analysis revealed that 70% of the selected clones showed reactivity with antibodies present in the relevant serum whereas the control strain expressing LamB without a *S. pyogenes* specific insert did not react with the same serum. In general, the rate of reactivity was observed to lie within the range of 35 to 75%. Colony PCR analysis showed that all selected clones contained an insert in the expected size range.

Subsequent sequencing of a larger number of randomly picked clones (600 to 1200 per screen) led to the identification of the gene and the corresponding peptide or protein sequence that was specifically

recognized by the human serum used for screening. The frequency with which a specific clone is selected reflects at least in part the abundance and/or affinity of the specific antibodies in the serum used for selection and recognizing the epitope presented by this clone. In that regard it is striking that clones derived from some ORFs (e.g. Spy0433, Spy2025) were picked more than 80 times, indicating their highly immunogenic property. Table 1 summarizes the data obtained for all 15 performed screens. All clones that are presented in Table 1 have been verified by Western blot analysis using whole cellular extracts from single clones to show the indicated reactivity with the pool of human serum used in the respective screen. As can be seen from Table 1, distinct regions of the identified ORF are identified as immunogenic, since variably sized fragments of the proteins are displayed on the surface by the platform proteins.

It is further worth noticing that most of the genes identified by the bacterial surface display screen encode proteins that are either attached to the surface of *S. pyogenes* and/or are secreted. This is in accordance with the expected role of surface attached or secreted proteins in virulence of *S. pyogenes*.

Example 4: Assessment of the reactivity of highly immunogenic peptide sequences with individual human sera.

Approximately 100 patients and 60 healthy adult sera were included in the analysis. Following the bioinformatic analysis of selected clones, corresponding peptides were designed and synthesized. In case of epitopes with more than 28 amino acid residues, overlapping peptides were made. All peptides were synthesized with a N-terminal biotin-tag and used as coating reagents on Streptavidin-coated ELISA plates.

The analysis was performed in two steps. First, peptides were selected based on their reactivity with the individual sera, which were included in the serum pools (five individual sera) used for preparations of IgG and IgA screening reagents for bacterial surface display. Peptides not displaying a positive reaction were not included in further, more detailed studies. Second, a large number of not pre-selected individual sera from patients with acute pharyngitis or with post-streptococcal diseases or from healthy adults and children were tested against the peptides showing specific and high reactivity with the screening sera. Antibody levels were measured by ELISA and compared by the score calculated for each peptide based on the number of positive sera and the extent of reactivity. An example for serum reactivity of 174 peptides representing *S. pyogenes* epitopes from the genomic screen with 20 human sera (representing 4 different pools of five sera) used for the antigen identification is shown in table 2. The peptides range from highly and widely reactive to weakly positive ones. Among the most reactive ones there are known antigens, some of them are also protective in animal challenge models for nasopharyngeal carriage (eg. C5a peptidase and M protein).

Example 5: Gene distribution studies with highly immunogenic proteins identified from *S. pyogenes*.

Gene distribution of group A streptococcal antigens by PCR. An ideal vaccine antigen would be an antigen that is present in all, or the vast majority of strains of the target organism to which the vaccine is directed. In order to establish whether the genes encoding the identified *Streptococcus pyogenes* antigens occur ubiquitously in *S. pyogenes* strains, PCR was performed on a series of independent *S. pyogenes* isolates with primers specific for the gene of interest. *S. pyogenes* isolates were obtained covering emm types most frequently present in patients as shown in Figure 4A. Oligonucleotide sequences as primers were designed for all identified ORFs yielding products of approximately 1,000 bp, if possible covering all identified immunogenic epitopes. Genomic DNA of all *S. pyogenes* strains was prepared as described under Example 2. PCR was performed in a reaction volume of 25 µl using Taq polymerase (1U), 200 nM dNTPs, 10 pMol of each oligonucleotide and the kit according to the manufacturers instructions (Invitrogen, The Netherlands). As standard, 30 cycles (1x: 5min. 95°C, 30x: 30sec. 95°C, 30sec. 56°C, 30sec. 72°C, 1x 4min. 72°C) were performed, unless conditions had to be adapted for individual primer pairs.

Results

All identified genes encoding immunogenic proteins were tested by PCR for their presence in 50 different strains of *S. pyogenes* (Figure 4A). As an example, figure 4B shows the PCR reaction for Spy0269 with all indicated 50 strains. As clearly visible, the gene is present in all strains analysed. The PCR fragment from strain no 8 (M89) was sequenced and showed that of 917 bp only 2 bp are different as compared to the *S. pyogenes* M1 strain SF310, resulting in only one amino acid difference between the two isolates.
From a total of 96 genes analysed, 70 were present in all strains tested, while 22 genes were absent in more than 10 of the tested 50 strains (Table 3). Several genes (Spy0433, Spy0681) showed variation in size and were not present in all strain isolates. Some genes showed variation in size, but were otherwise conserved in all tested strains (e.g. Spy1371). Sequencing of the generated PCR fragment from one strain and subsequent comparison to the M1 strain confirmed the amplification of the correct DNA fragment and revealed a degree of sequence divergence as indicated in Table 3. Importantly, many of the identified antigens are well conserved in all strains in sequence and size and are therefore novel vaccine candidates to prevent infections by group A streptococci.

Example 6: Characterization of immune sera obtained from mice immunized with highly immunogenic proteins/peptides from *S. pyogenes* displayed on the surface of *E. coli*.

Generation of immune sera from mice
E. coli clones harboring plasmids encoding the platform protein fused to a *S. pyogenes* peptide, were grown in LB medium supplemented with 50μg/ml Kanamycin at 37°C. Overnight cultures were diluted 1:10, grown until an OD_{600} of 0.5 and induced with 0.2 mM IPTG for 2 hours. Pelleted bacterial cells were suspended in PBS buffer and disrupted by sonication on ice, generating a crude cell extract. According to the OD_{600} measurement, an aliquot corresponding to $5x10^7$ cells was injected into NMRI mice i.v., followed by a boost after 2 weeks. Serum was taken 1 week after the second injection. Epitope specific antibody levels were measured by peptide ELISA.

In vitro expression of antigens
Expression of antigens by *in vitro* grown *S. pyogenes* SF370/M1 was tested by immunoblotting. Different growth media and culture conditions were tested to detect the presence of antigens in total lysates and bacterial culture supernatants. Expression was considered confirmed when a specific band corresponding to the predicted molecular weight and electrophoretic mobility was detected.

Cell surface staining
Flow cytometric analysis was carried out as follows. Bacteria were grown under culture conditions, which resulted in expression of the antigen as shown by the immunoblot analysis. Cells were washed twice in Hanks Balanced Salt Solution (HBSS) and the cell density was adjusted to approximately 1 X 10^6 CFU in 100μl HBSS, 0.5% BSA. After incubation for 30 to 60 min at 4°C with antisera diluted 50 to 100-fold, unbound antibodies were washed away by centrifugation in excess HBSS, 0.5% BSA. Secondary goat anti-mouse antibody ($F(ab')_2$ fragment specific) labeled with fluorescein (FITC) was incubated with the cells at 4°C for 30 to 60 min. After washing the cells, antibodies were fixed with 2% paraformaldehyde. Bound antibodies were detected using a Becton Dickinson FACScan flow cytometer and data further analyzed with the computer program CELLQuest. Control sera included mouse pre-immune serum and mouse polyclonal serum generated with lysates prepared from IPTG induced *E. coli* cells transformed with plasmids encoding the genes *lamB* or *fhuA* without *S. pyogenes* genomic insert.

Opsonophagocytosis assay
Epitope specific immune sera were tested for their activity to induce opsonophagocytosis in a FACS based assay. Sera were heat inactivated and anti-*E. coli* antibodies then removed by incubation with whole cell *E. coli* (3x). 10^7 Alexa 488 labeled *S. pyogenes* cells were pre-opsonized in the presence of 2-10% immune serum and 2% hamster serum as complement source and then added to 10^6 phagocytic cells (RAW246.7 or P388.D1 murine monocytic cell lines). The cell mixture was incubated for 30 min at 37°C. Time, IgG concentration and complement dependent uptake of bacteria was registered as an increase in mean fluorescence intensity of the phagocytic cells measured with a fluorescence activated cell sorter.

Bactericidal (killing) assay
Murine macrophage cells (RAW246.7 or P388.D1) and bacteria were incubated and the loss of viable bacteria after 60 min was determined by colony counting. In brief, bacteria were washed twice in Hanks Balanced Salt Solution (HBSS) and the cell density was adjusted to approximately 1X 10^5 CFU in 50µl HBSS. Bacteria were incubated with mouse sera (up to 25%) and guinea pig complement (up to 5%) in a total volume of 100µl for 60min at 4°C. Pre-opsonized bacteria were mixed with macrophages (murine cell line RAW264.7 or P388.D1; 2X 10^6 cells per 100µl) at a 1:20 ratio and were incubated at 37°C on a rotating shaker at 500 rpm. An aliquot of each sample was diluted in sterile water and incubated for 5 min at room temperature to lyse macrophages. Serial dilutions were then plated onto Todd-Hewitt Broth agar plates. The plates were incubated overnight at 37°C, and the colonies were counted with the Countermat flash colony counter (IUL Instruments). Control sera included mouse pre-immune serum and mouse polyclonal serum generated with lysates prepared from IPTG induced *E. coli* transformed with plasmids harboring the genes *lamB* or *fhuA* without *S. pyogenes* genomic insert.

Results

In vitro expression and cell surface staining. The expression of the antigenic proteins was analyzed *in vitro* in *S. pyogenes* SF370/M1 by using sera raised against *E. coli* clones harboring plasmids encoding the platform protein fused to a *S. pyogenes* peptide. This analysis served as a first step to determine whether a protein is expressed at all in order to evaluate surface expression of the polypeptide by FACS analysis. It was anticipated that not all protein would be expressed under *in vitro* conditions, but several proteins were detected by Western blot analysis in total cell lysates (e.g. Spy0012, Spy0112, Spy0416, Spy0437, Spy0872, Spy1032, Spy1315, Spy1798; data not shown). Cell surface accessibility for several antigenic proteins was subsequently demonstrated by an assay based on flow cytometry. Streptococci were incubated with preimmune and polyclonal mouse sera raised against *S. pyogenes* lysate or *E. coli* clones harboring plasmids encoding the platform protein fused to a *S. pyogenes* peptide, follow by detection with fluorescently tagged secondary antibody. As shown in Fig. 5A, antisera raised against *S. pyogenes* lysate cause a shift in fluorescence of the *S. pyogenes* SF370/M1 cell population. Similar cell surface staining of *S. pyogenes* SF370/M1 cells was observed with polyclonal sera raised against peptides of antigen Spy0012 (Fig. 5B), Spy1315 and Spy1798 (Fig. 5C), although only a subpopulation of the bacteria was stained, as indicated by the detection of two peaks. This phenomenon may be a result of differential expression of the gene products during the growth of the bacterium or partial inhibition of antibody binding caused by other surface molecules.
These experiments confirmed the bioinformatic prediction that these proteins are exported due to their signal peptide sequence and in addition showed that they are anchored on the cell surface of *S. pyogenes* SF370/M1. They also confirm that these proteins are available for recognition by human antibodies and make them valuable candidates for the development of a vaccine against Group A Streptococcal disease.

Example 7: Protective immune responses against infection with group A streptococci upon immunization with recombinant antigens.

Experimental procedures

Cloning of genes encoding antigenic proteins
The gene or DNA fragment of interest was amplified from genomic DNA of *S. pyogenes* SF370 by PCR amplification using gene specific primers. Apart from the gene specific sequence, the primers contained additional bases at the respective 5' end consisting of restriction sites that aided in the directional cloning of the amplified PCR product. The gene specific sequence of the primer ranged between 15-24 bases in length. The PCR products obtained were digested with the appropriate restriction enzymes and cloned into the appropriately digested pET28b(+) vector (NOVAGEN). After confirmation of the construction of the recombinant plasmid, *E. coli* BL21 STAR® cells (INVITROGEN) that served as expression hosts were transformed. These cells are optimized to efficiently express the gene of interest as encoded by the pET28b plasmid.

Expression of antigens in Escherichia coli

E. coli BL21 STAR® cells harboring the recombinant plasmid were grown into log phase in LB medium supplemented with 50µg/ml Kanamycin at 37°C. Once an OD_{600nm} of 0.8 was reached, the culture was induced with 1 mM IPTG for 3 hours at 37°C. The cells were harvested by centrifugation, lysed by a combination of the freeze-thaw method followed by disruption of cells with the Bug-buster® reagent from NOVAGEN. The lysate was separated by centrifugation into soluble (supernatant) and insoluble (pellet) fractions.

Purification of recombinant proteins from E. coli

Depending on the localization of the protein, different purification strategies were followed. Proteins in the soluble fraction were purified by binding the supernatant of the cell lysates after cell disruption to Ni-Agarose beads (Ni-NTA-Agarose®, QIAGEN). Due to the presence of the penta-Histidine (HIS) at the C, N or both termini of the expressed protein, the protein binds to Ni-agarose while other contaminating proteins are washed and removed from the column by washing buffer. The proteins were eluted by a solution containing 100 mM imidazole in the appropiate buffer. The eluate was concentrated, assayed by Bradford for protein concentration and analysed by SDS-PAGE and Western blot. Proteins in the insoluble fraction were purified by solubilization of the pellet in an appropriate buffer containing 8 M Urea. The purification was performed under denaturing conditions (in buffer containing 8M Urea) using the same materials and procedure as mentioned above for soluble proteins. The eluate was concentrated and dialyzed to remove all urea in a gradual or stepwise manner. The final protein solution was concentrated, analysed by SDS-PAGE and measured by Bradford method. Expression was considered confirmed when a specific band corresponding to the predicted molecular weight and electrophoretic mobility was detected. For proteins, which precipitated during dialysis due to the removal of the denaturing reagent urea, the insoluble inclusion bodies were washed several times and directly used for immunization of mice.

Immunisation of NMRI mice with recombinant proteins and challenge with S. pyogenes AP1

The immunogenicity of the proteins was assayed in an experimental animal model using NMRI mice and the *S. pyogenes* strain AP1 as infectious agent. Ten female NMRI mice at 7-8 weeks of age were immunized with 50µg/dose of recombinant protein every 2 weeks for a total of 3 doses. The initial dose was adjuvanted with Complete Freund's adjuvant while the remaining two doses were adjuvanted with Incomplete Freund's adjuvant. At the end of the immunization the mice were bled to check the antibody titer and subsequentely intravenously (i.v.) challenged with a lethal dose of *S. pyogenes* AP1 (5x 10^7 pathogenic bacteria). The mice were scored for 18 to 21 days post challenge for survival.

Results

Expression and purification of recombinant proteins.

Of the 31 proteins selected for recombinant protein expression, 29 proteins could be produced in *E. coli* to a level sufficient for purification. While some of the proteins could be produced as soluble protein (see Table 4), some proteins turned out to be insoluble (*e.g.* Spy416B, Spy0872) or precipitated upon dialysis, which was intended to remove the denaturing reagent urea after solubilization of insoluble proteins such as Spy0031, Spy0292, Spy720. In these cases the washed inclusion bodies were directly injected into mice for immunization. In generell, the affinity purification yielded a recombinant protein preparation of at least 85% purity.

Immune responses after immunization with recombinant proteins in NMRI mice.

Table 4 lists those antigens, which were tested in mice and showed some degree of protection in experimental animals. Recombinant proteins, which were also tested in the bacteremia model in animals, but did show not any level of protection in the described experiments are not listed here; but include proteins such as Spy0012, Spy1063 and Spy1494. The described bacteremia model evaluates the protective value of vaccine candidates against invasive disease as pathogenic bacteria are directly injected into the blood. Recombinant proteins, which induce antibodies capable of protection against such group A streptococcal infection, are considered as valuable candidates for the development of a vaccine against

Group A Streptococcal disease. In comparison to the positive control Spy2018 (M1 protein), which was previously shown to provide protection against *S. pyogenes* challenge, a number of antigens performed to a similar degree when the endpoint of the challenge experiment after 18 or 21 days (Table 4) was assessed (Spy0416, Spy1607 or Spy0292). Other proteins showed only a partial protective effect (Spy0720, Spy0872), but may prove very effective when combined with other antigens (Fig. 6).
Surprisingly, the antigen screen had identified immunogenic epitopes predominantly in the first half of the two larger proteins, Spy0416 and Spy1972. Therefore it was reasoned that the protective region may also be contained in the N terminal part of the protein. In case of Spy0416, both parts of the antigen were produced as recombinant protein (Spy0416A and Spy0416B; see Table4) and tested in animal experiments. The experiments showed that only the first half of the protein Spy0416 (Table 4; Spy0416A) provided protection in the animal model, while the second half of the protein (Spy0416B) had no protective effect at all, clearly delineating a smaller region within the protein as the vaccine candidate. For antigen Spy1972 only the first half of the full-length protein was produced as recombinant protein and tested in the animal model.

Example 8: Variability of genes encoding antigenic proteins in *S. pyogenes* strains of various serotypes.

Experimental procedures

Sequencing of PCR fragments and bioinformatic analysis.

The PCR analysis of *S. pyogenes* strains is described in Example 5. The sequencing of the PCR fragments provided an estimate of the variability of the gene and the summary of the results are listed in Table 3. The availability of genomic sequences from five *Streptococcus pyogenes* strains (SF370: M1; MGAS8232: M18; SSI-1: M3; MGAS315: M3; Manfredo: M5) allowed a further assessment of the variability of the antigens. All sequences were aligned with the respective antigen sequence from *S. pyogenes* SF370 and those amino acid residues identified which differed from the ones in the antigenic protein from *S. pyogenes* SF370. Inserted or deleted sequences were detected in some of the antigenic proteins, but are not contained in this analysis.

Results

Table 5 shows all positions that were identified to be variable in the indicated antigens in one of the four *S. pyogenes* strains (MGAS8232: M18; SSI-1: M3; MGAS315: M3; Manfredo: M5) or the strain used for sequencing of the amplified PCR fragment (see Table 3). The bioinformatic analysis shows that some of the antigenic proteins are very well conserved without a single amino exchange in any of the six strains of serotypes M1, M3, M5, M18 and M89. Proteins belonging to this group include Spy0103 and Spy1536, while the exchanges in the other antigenic proteins are more numerous in larger proteins than in smaller ones, as expected from the difference in size by itself. Although a variety of strains was analysed, it was almost never observed that a single residue was changed to more than one other amino acid in the other strains. A further analysis of sequences of the respective genes in a larger number of strains of varying serotypes, clinical indication or geographic location would certainly identify possible changes in those amino acid residues listed or in additional residues.
Only one of the antigenic proteins analysed by the alignment of six gene sequences showed a considerable degree of variation in size (Spy1357: SF370 - 217 amino acids; MGAS8232 – 245 aa; SSI-1 – 329 aa; MGAS315 – 329 aa; Manfredo – 279 aa). Thus it is evident, that most of the evaluated antigens are very well conserved in sequence as well as in size and provide promising candidates for vaccine development.

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Table 1: Immunogenic proteins identified by bacterial surface display.

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
Spy0012	Hypothetical protein	4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425	A:12, I:5, N:2	1-114	1, 151
Spy0019	putative secreted protein (cell division and antibiotic tolerance)	5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395	F:2, I:16, K:24, N:29, P:12	29-226	2, 152
Spy0025	putative phosphoribosylformylglycinamidine synthase II	4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254	D:3	919-929	3, 153
Spy0031	putative choline binding protein	5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360	I:3, K:3, N:3	145-305	4, 154
Spy0103	putative competence protein	15-39, 52-61, 72-81, 92-97	A:8	71-81	5, 155
Spy0112	putative pyrroline carboxylate reductase	13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245	B:4	173-186	6, 156
Spy0115	putative glutamyl-aminopeptidase	5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352	A:3, C:26	316-331	7, 157
Spy0166	Hypothetical protein	6-28, 43-53, 60-76, 93-103	I:22, K:7, N:17, O:31, P:5	21-99	8, 158
Spy0167	Streptolysin O	10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568	A:118, B:14, C:18, D:37, F:141, G:79, H:92, I:97, K:123, L:5, M:21, N:225, O:230, P:265	9-264	9, 159
Spy0168	Hypothetical protein	5-29, 39-45, 107-128	K:4, N:7	1-112	10, 160

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
Spy0171	hypothetical protein	4-38, 42-50, 54-60, 65-71, 91-102	H:2	21-56	11, 161
Spy0183	putative glycine betaine/proline ABC transporter	4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391	C:6	23-39	12, 162
Spy0230	putative ABC transporter (ATP-binding protein)	6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591	C:46	474-489	13, 163
Spy0269	putative surface exclusion protein	8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864	A:2, B:12, D:3, F:11, H:5, N:6	37-241 409-534 582-604 743-804	14, 164
Spy0287	conserved hypothetical protein	4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416	K:1	202-337	15, 165
Spy0292	penicillin-binding protein (D-alanyl-D-alanine car	4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407	F:2	1-48	16, 166
Spy0295	oligopeptidepermease	18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297	A:3	203-217	17, 167
Spy0348	putative aminodeoxychorismate lyase	20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521	D:5, I:3, M:3, P:3	261-273	18, 168
Spy0416	putative cell envelope serine proteinase	6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-	A:3, B:4, C:30, D:13, F:138, G:120, H:101, I:9, K:14, M:2, N: 15, O:8, P:19	1-414 443-614 997-1392	19, 169

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641			
Spy0430	hypothetical protein	14-42, 70-75, 90-100, 158-181	B:7, I:10, P:18	1-164	20, 170
Spy0433	hypothetical protein	4-21, 30-36, 54-82, 89-97, 105-118, 138-147	A:138, B:8, C:67, D:11, E:13, F:35, G:10, H:5, M:8	126-207	21, 171
Spy0437	Hypothetical protein	4-21, 31-66, 96-104, 106-113, 131-142	A:29, B:10, C:21, D:24, E:15	180-204	22, 172
Spy0469	putative 42 kDa protein	5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386	B:5, F:77, I:8, K:15, M:3, N:17, O:20	11-197 204-219 258-372	23, 173
Spy0488	hypothetical protein	4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322	A:17, B:11, C:23, D:12, E:4, G:4, H:7	195-289	24, 174
Spy0515	Putative sugar transferase	4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329	B:5, I:3	12-130	25, 175
Spy0580	conserved hypothetical protein	10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707	C:5	434-444	26, 176
Spy0621	conserved hypothetical protein	6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430	C:3	360-375	27, 177
Spy0630	putative PTS dependent N-acetyl-galactosamine-IIC	4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203-237, 245-251	C:2	254-260	28, 178
Spy0681	hypothetical protein, phage associated	12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400	A:8	369-382	29, 179
Spy0683	putative minor capsid protein, phage associated	11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300,	B:11, D:4	270-312	30, 180

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487			
Spy0702	Hypothetical protein	5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604	L:2	486-598	31, 181
Spy0710	conserved hypothetical protein, phage associated	4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374	B:10	378-396	32, 182
Spy0711	pyrogenic exotoxin C precursor, phage associated (speC)	5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184	K:2	75-235	33, 183
Spy0720	conserved hypothetical protein	6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310	D:2	30-51	34, 184
Spy0727	putative DNA gyrase, subunit B	17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647	M:26	208-219	35, 185
Spy0737	putative extracellular matrix binding protein	4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039	B:5, E:3, K:11	396-533 1342-1502 1672-1920	36, 186
Spy0747	extracellular nuclease	4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-	A:72, B:17, H:6, O:3	1-113 210-232	37, 187

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905		250-423 536-564	
Spy0777	putative ATP-dependent exonuclease, subunit A	4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201	C:4, E:2	617-635	38, 188
Spy0789	putative ABC-transporter (permease protein	7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244	A:3	190-203	39, 189
Spy0839	putative glycerophosphodiester phosphodieste	4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574	A:7, D:2	385-398	40, 190
Spy0843	cell surface protein	5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003	A:11, B:3, C:5, D:4, F:50, H:19, G:49, I:112, K:102, L:10, M:3, N:213, O:188, P:310	12-190 276-283 666-806	41, 191
Spy0872	putative secreted 5'-nucleotidase	4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664	A:6, D:2, F:5, H:14, I:9, K:10, L:1, N:16, O:12	30-80 89-105 111-151	42, 192
Spy0895	histidine protein kinase	7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259	C:11	195-203	43, 193
Spy0972	putative terminase, large subunit - phage	5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134,	B:2	32-50	44, 194

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426			
Spy0981	hypothetical protein - phage associated	8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174	A:7, B:2	75-90	45, 195
Spy1008	streptococcal exotoxin H precursor (speH)	4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233	C:11	69-88	46, 196
Spy1032	extracellular hyaluronate lyase	4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802	B:3, K:3, M:5	96-230 361-491 572-585	47, 197
Spy1054	putative collagen-like protein (SclC)	4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289	A:71, B:13, C:233, D:41, E:163, F:200, G:442, H:129, N:3	102-210	48, 198
Spy1063	putative periplasmic-iron-binding protein	13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313	A:4	240-248	49, 199
Spy1162	putative ribonuclease HII	5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260	B:3, C:5	182-198	50, 200
Spy1206	putative ABC transporter	10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504	A:2	41-56	51, 201
Spy1228	Putative lipoprotein	5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333	M:33	202-217	52, 202
Spy1245	putative phosphate ABC transporter	6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283	I:3, K:3	1-127	53, 203
Spy1315	hypothetical protein	4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718	B:4	297-458	54, 204
Spy1357	protein GRAB (protein G-related	5-43, 92-102, 107-116, 120-130, 137-144, 155-163,	G:27, H:8, K:2,	24-135	55, 205

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
	alpha 2M-binding p	169-174, 193-213	N:4		
SPy1361	putative internalin A precursor	4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721	F:21, G:26, H:6, K:4, N:5	176-330	56, 206
Spy1371	putative NADP-dependent glyceraldehyde-3-phosphate dehydrogenase	31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472	D:14, H:3	46-62 296-341	57, 207
Spy1375	putative ribonucleotide reductase alpha-c	23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716	A:2	667-684	58, 208
Spy1389	putative alanyl-tRNA synthetase	20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869	B:2, P:3	258-416	59, 209
Spy1390	putative protease maturation protein	7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300	A:3, B:2, D:3	278-295	60, 210
Spy1422	putative recombination protein	4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191	C:2	183-195	61, 211
Spy1436	putative deoxyribonuclease	12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241	K:1	63-238	62, 212
Spy1494	hypothetical protein	4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308	G:3, I:5, K:6, M:5, N:10, O:6, P:4	1-141	63, 213
Spy1523	cell division protein	11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379	I:2	231-368	64, 214
Spy1536	conserved hypothetical protein	9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342	A:19, C:3	247-260	65, 215

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
Spy1564	conserved hypothetical protein	7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279	C:4	64-72	66, 216
Spy1604	conserved hypothetical protein	4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897	B:2, K:2	222-362 756-896	67, 217
Spy1607	conserved hypothetical protein	11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255	D:5	153-170	68, 218
Spy1615	putative late competence protein	4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212	C:4	56-73	69, 219
Spy1666	conserved hypothetical protein	4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334	D:2	298-312	70, 220
Spy1727	conserved hypothetical protein	7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238, 247-254	B:5	141-157	71, 221
Spy1785	putative ATP-dependent DNA helicase	23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663	D:3	433-440 572-593	72, 222
Spy1798	hypothetical protein	4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267	A:12, I:12, K:7, N:17, O:13, P:8	17-319 417-563	73, 223
Spy1801	immunogenic secreted protein precursor homolog	6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-	H:2, I:8, K:6, N:11	46-187	74, 224

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500			
Spy1813	hypothetical protein	4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992	I:16, K:12, N:6	21-244 381-499 818-959	75, 225
Spy1821	putative translation elongation factor EF-P	19-29, 65-75, 90-109, 111-137, 155-165, 169-175	C:6	118-136	76, 226
Spy1916	putative phospho-beta-D-galactosidase	15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465	C:8	147-155	77, 227
Spy1972	Pullulanase	11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161	A:6, I:2, K:5, N:9	74-438	78, 228
Spy1979	streptokinase A precursor	4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413	I:6, M:3, N:10	156-420	79, 229
Spy1983	collagen-like surface protein (SclD)	4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343	A:81, B:24, F:19, G:41, I:2, K:2	79-348	80, 230
Spy1991	anthranilate synthase component II	12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168	D:2	53-70	81, 231
Spy2000	surface lipoprotein	4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522	B:3, N:2	183-341	82, 232
Spy2006	hypothetical protein	4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-	A:15, B:9, C:5, D:3, F:18, G:25, H:5, M:10, N:5	92-231 618-757	83, 233

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822			
Spy2009	hypothetical protein	11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372	B:2, I:7, K:7, P:2	41-170	84, 234
Spy2010	C5A peptidase precursor	6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174	A:47, B:10, D:3, F:48, G:20, H:4, I:6, K:13, M:5, N:10, P:6	20-487 757-1153	85, 235
Spy2016	inhibitor of complement (Sic)	10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305	A:11, B:38, C:16, F:56, G:27, H:13, K:5, N:2, O:3, P:14	26-74 91-100 105-303	86, 236
Spy2018	M1-Protein	9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480	A:316, B:26, C:107, D:12, E:49, F:88, G:118, H:6, I:7, K:2, M:48, N:4	10-223 231-251 264-297 312-336	87, 237
Spy2025	immunogenic secreted protein precursor	5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537	F:7, G:16, H:7, K:63, L:2, N:18, O:42	22-344	88, 238
Spy2039	pyrogenic exotoxin B	5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395	I:15, K:3, N:12	1-151	89, 239
Spy2043	mitogenic factor MF1 (speF)	6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-	K:1	91-263	90, 240

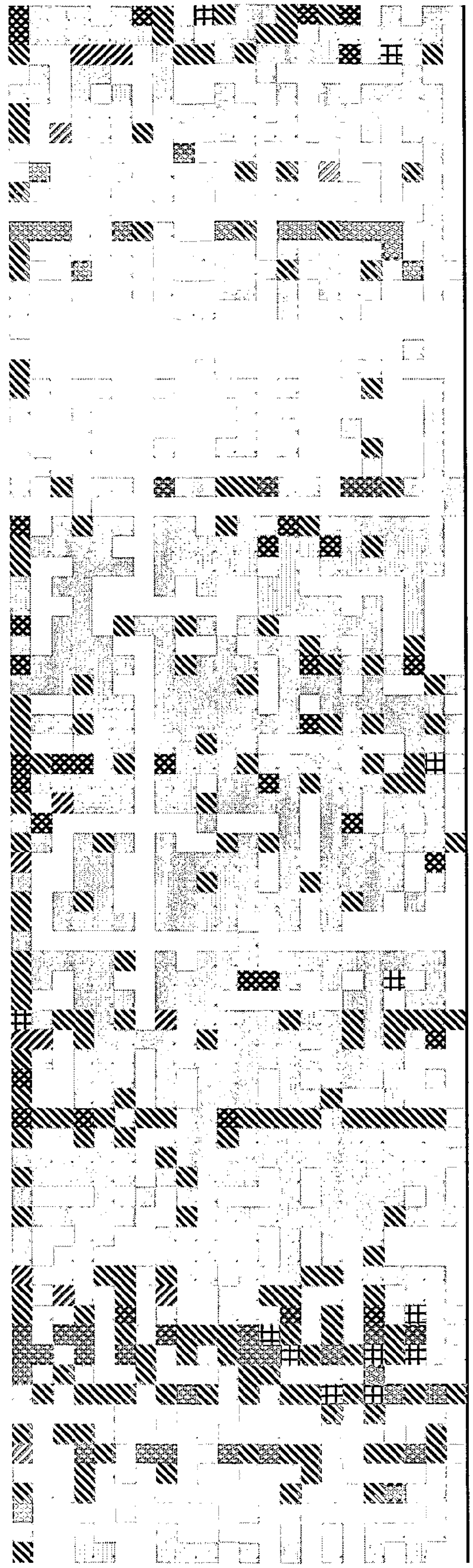
S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756			
Spy2059	penicillin-binding protein 2a	4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775	D:2, E:2	261-272	91, 241
Spy2110	putative anaerobic ribonucleoside-triphosphate reductase	4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701	E:7	541-551	92, 242
Spy2127	Hypothetical protein	6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252	I:6, P:2	84-254	93, 243
Spy2191	hypothetical protein	13-30, 71-120, 125-137, 139-145, 184-199	C:20, E:3, M:5	61-78	94, 244
Spy2211	transmembrane protein	9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855	A :3	568-580	95, 245
ARF0450	no homology	11-21, 29-38	A:11	5-17	96, 246
ARF0569	no homology	none	A:2	2-9	97, 247
ARF0694	no homology	4-10, 16-28	B:7, D:3, M:3	7-18 26-34	98, 248
ARF0700	No homology	10-16	M:11	1-15	99, 249
ARF1007	No homology	none	B:2	4-11	100, 250
ARF1145	No homology	4-40, 42-51	C:9	37-53	101, 251
ARF1208	no homology	4-21	C:1	22-29	102, 252

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
ARF1262	No homology	none	D:2	2-11	103, 253
ARF1294	39% with SA0131 (first 28 aa of 67 aa protein)	9-17, 32-44	D:2	1-22	104, 254
ARF1316	no homology	19-25, 27-32	E:19	15-34	105, 255
ARF1352	38% with SA1142 (aa 265-295 of 358 protein)	4-12, 15-22	D:4	11-33	106, 256
ARF1481	No homology	10-17, 24-30, 39-46, 51-70	C:2	51-61	107, 257
ARF1557	No homology	none	C:2	6-19	108, 258
ARF1629	36% with SP0069 (aa 139-169 of 211 aa protein)	6-11, 21-27, 31-54	A:4, B:6	11-29	109, 259
ARF1654	no homology	4-10, 13-45	A:2	11-35	110, 260
ARF2027	no homology	4-14, 23-32	D:2	11-35	111, 261
ARF2093	putative elongation factor TS	14-39, 45-51	C:3	15-29	112, 262
ARF2207	38% with SP1006 (aa 7-37 of 67 aa protein)	4-11, 14-28	A:117	4-17	113, 263
CRF0038	No homology	4-16	C:6	2-16	114, 264
CRF0122	No homology	4-10, 12-19, 39-50	C:2	6-22	115, 265
CRF0406	no homology	none	D:5, E:11	2-13	116, 266
CRF0416	No homology	4-11, 22-65	C:42	3-19	117, 267
CRF0507	No homology	17-23, 30-35, 39-46, 57-62	B:3, C:4	30-49	118, 268
CRF0549	No homology	4-19	C:6	14-22	119, 269
CRF0569	No homology	none	N:35	2-9	120, 270
CRF0628	34% (14 of 41) with conserved hypothetical protein of P. aeruginosa	7-18, 30-43	A:3	4-12	121, 271
CRF0727	40% (16 of 40) with transcriptional regulator of S. pneumoniae (70 aa, SP0584)	4-30, 39-47	N:6	5-22	122, 272
CRF0742	33% with SA0422 (aa 11-37 of 42 aa protein, listed as 280 aa protein)	6-15	D:7, E:12	14-29	123, 273
CRF0784	No homology	4-34	N:9	23-35	124, 274
CRF0854	No homology	4-36, 44-57, 65-72	N:14	14-27	125, 275
CRF0875	no homology	4-18	A:4, D:1	11-20	126, 276
CRF0907	Homology to lysosomal trafficking regulator LYST [Homo sapiens]	none	A:39	5-19	127, 277

S. pyogenes antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
CRF0979	no homology	18-36	D:21	6-20	128, 278
CRF1068	no homology	4-10, 19-34, 41-84, 96-104	C:1, D:3	50-63	129, 279
CRF1152	No homology	4-9, 19-27	C:15	8-21	130, 280
CRF1203	No homology	4-16, 18-28	N:3	22-30	131, 281
CRF1225	No homology	4-15	C:8	21-35	132, 282
CRF1236	No homology	4-17	N:3	3-13	133, 283
CRF1362	No homology	4-12	C:6	4-18	134, 284
CRF1524	no homology	4-24, 31-36	D:3	29-45	135, 285
CRF1525	No homology	12-22, 34-49	C:2	21-32	136, 286
CRF1527	no homology	4-17	D:4, E:1	22-32	137, 287
CRF1588	No homology	4-16, 25-42	C:2	7-28	138, 288
CRF1649	No homology	4-10	C:3	7-20	139, 289
CRF1749	No homology	4-11, 16-36, 39-54	C:15	28-44	140, 290
CRF1903	no homology	5-20, 29-54	A:14	14-29	141, 291
CRF1964	no homology	24-33	A:8	10-22	142, 292
CRF2055	no homology	10-51, 54-61	B:1, F:12, H:14	43-64	143, 293
CRF2091	No homology	7-13	C:2	2-17	144, 294
CRF2096	No homology	11-20	C:4	6-20	145, 295
CRF2104	No homology	4-30, 34-41	C:2	19-28	146, 296
CRF2116	No homology	n.d.		11-21	147, 297
CRF2153	no homology	4-16, 21-26	F:2	9-38	148, 298
NRF0001	ARF in Oligo ABC transporter (not annotated by TIGR), 33% with SA0643 (aa 107-162 of 469 aa protein)	4-12, 15-27, 30-42, 66-72	A:7, B:1	10-24	149, 299
NRF0003	no homology	8-17	A:23	11-20	150, 300

Table 2-1

Peptide	Peptide sequence	Seq. ID	location in protein (aa)	score	+	++	+++	++++
SPA0450.1	SRFLPTRRDYSSLWSASC	246	2-19	13	13			
SPA0569.1	SFIWEKRNPEGS	247	1-12	7	7			
SPA0694.2	KTSQTIPTKRQKMRRTMT	248	21-38	15	11	2		
SPA1294.1	MLKAKKTNSKLVTLSQPTKKF	254	2-22	7	7			
SPA1316.1	GRTRHDHVNCYSRNGICSP	255	15-33	17	15	1		
SPA1352.1	QPKHKEQPVLKMLKNYESKKQI	256	11-32	2	2			
SPA1629.1	RDANDCQRTGFSKCDFSW	259	11-28	35	10	11	1	
SPA1654.1	MIQINTPLSILFPNTLVQ	260	10-27	10	7		1	
SPA2027.1	PFLKWLRSAKNNSKDIRC	261	9-26	18	11	2	1	
SPA2207.1	VKDVWSTLKIWER	263	4-16	35	10	11	1	
SPC0406.1	QAPLDDHHNKPTYWSGYL	266	1-18	16	11	1	1	
SPC0742.1	KYKSHKERLTINTFKRQG	273	12-29	31	10	4	3	
SPC0875.1	WHYQLKLSQVQTMTFPPL	276	6-23	5	5			
SPC0907.1	RNLLDHFLRNNPHQNHKAKLD	277	1-21	15	7	1	2	
SPC1068.1	FGHIDLSNASINNNQVRS	279	47-64	19	7	3	2	
SPC1524.1	LLNRGANISSQKVIKEVR	285	28-45	23	13	2	2	
SPC1527.1	TLKRFTFDTINFFDDNFW	287	18-35	13	9	2		
SPC1903.1	KPLVKVPENRTMAPPNPP	291	14-31	23	10	5	1	
SPC1964.1	HQIGQKWKKERPKPTWSK	292	7-24	32	11	9	1	
SPN0001.1	TQQLFRKPSLSNNLLKHL	299	8-25	29	12	7	1	
SPN0003.1	SGRQDSNLRHLGPKPSTLPS	300	1-20	5	5			
SPO0012.1	PVISTEKKLIFSKNAV	151	18-33	24	10	7		
SPO0012.2	AYKDSDLTLPA	151	62-72	31	12	8	1	
SPO0019.1	INALLNSKSISDVV	152	118-131	17	9	4		
SPO0031.1	DPSGTYHFTTRLPVKGQTSIDSPDLA	154	195-220	4	4			
SPO0031.2	DSPDLAYYEAGQSVYYDKVVTAGGYT	154	215-240	7	7			
SPO0031.4	PIKEPAQSVVQNDNTKPSIKVGDTVT	154	255-280	1	1			
SPO0103.1	KPSLSQLKAD	155	72-81	19	17	1		
SPO0112.1	EALAKAGVKNGIP	156	174-186	9	9			
SPO0115.1	YIHSHQTLYAMDDFV	157	317-331	24	16	4		
SPO0166.1	LEMSNSGQALDIYQAVQTLNAENML	158	35-59	16	14	1		
SPO0166.2	NAENMLLNYYESLPFYLNRQSILANMTKALK	158	54-84	10	10			
SPO0166.3	MTKALKDAHIREAMAHYKLGEFAHYQ	158	79-104	16	10	1		
SPO0167.1	SNKQNTASTETTTTNEQPKPESSELT	159	33-58	21	18		1	
SPO0167.2	KEMPLESAEKEEKKSEDKKKS	159	81-101	17	11	3		
SPO0167.3	PKEGVKKADKFIVIE	159	136-150	18	16	1		
SPO0167.4	TYPAALQLANKGFT	159	173-186	3	3			
SPO0167.5	NLVNQWHDNYSGGNTLPARTQ	159	231-251	36	11	6	3	1
SPO0171.1	TPHHQTVHASDVTLTETCDKNGTVCFG	161	22-48	5	3	1		
SPO0183.1	MVKTGKNKSEIFKKTG	162	24-39	6	6			
SPO0230.1	MSLPKGYNTYVSDDD	163	475-489	34	11	10	1	
SPO0269.1	DRASGETKASNTHDDSLPK	164	38-56	13	11	1		
SPO0269.2	TLKQSDSINLQVRQINDTKGSL	164	583-604	40	8	6	4	2
SPO0287.1	EVIAQAGSQIKFSAIDRLGPSVTTY	165	202-223	2		2		
SPO0287.2	PSVTTYISRRGRLEKDANIDWALAVM	165	222-247	18	14	2		
SPO0287.3	WALAVMNEGNVIADFDSDLIGQGSQA	165	242-267	7	7			
SPO0287.4	GQGSQADLKVVAASSGRQVQGIDTRV	165	262-287	17	15	1		
SPO0287.5	GIDTRVTNYGQRTVGHILQHGVILER	165	282-307	1	1			
SPO0287.6	GVILERGTLTFNGIGHILKDAKGADA	165	302-327	16	14	1		
SPO0292.1	YSVTAKHAIAVDLESGKVLYEKDA	166	25-48	12	8	2		
SPO0295.1	SQTLGTPMYKIAVK	167	204-217	2	2			
SPO0348.1	EGGTAEPTKPSLGKILIP	168	259-276	26	11	1	3	1
SPO0416.1	PVNTDVHDWVKTKGAWDKG	169	121-139	33	12	9	1	
SPO0416.2	DGSHDIDW	169	260-267	31	12	8	1	
SPO0416.4	EDFDEDWENFEFDAEAEPKAIKKHKI	169	215-240	24	9	2	3	
SPO0430.1	GQHKRDPLETEAEDDSQGGRQEGRQ	170	115-140	12	10	1		
SPO0437.1	KFWHQRLSENIQDQWWNFKGLFQ	172	182-204	11	9	1		
SPO0469.1	DVPTTPFASA	173	144-153	19	14	1	1	
SPO0469.2	KTDISEAPTSANRPV	173	205-219	25	13	6		
SPO0488.1	INPKGRQATIT	174	196-206	2	2			
SPO0488.2	TPGIPGKFKR	174	240-249	19	13	3		
SPO0488.3	NIKVIDEKSTGRFEPF	174	272-287	12	8	2		
SPO0488.4	KGRQATITYGDGSTDIIPPAVLWKK	174	199-223	25	15	2	2	
SPO0488.5	AVLWKKGSVKEPTEADQSVG	174	218-237	14	12	1		
SPO0515.1	GDVYEGAMTGADAFFFPSREETEG	175	226-249	6	6			
SPO0515.2	GFIEALKKVFSGASNKVEAG	175	287-306	21	17	2		
SPO0580.1	IARRLQDPLAELVKIDPKSI	176	430-449	17	7	5		
SPO0621.1	LENPRTQIEMMQKDG	177	361-375	14	12	1		
SPO0630.1	NKPKQVDATTVQGGQQDDWI	178	241-260	16	14	1		
SPO0702.1	ALVRKDGTHTAFVHFSNATP	181	483-502	28	10	6	2	
SPO0710.1	NYLGIGQTDKDGNRISLW	182	379-396	20	12	4		
SPO0720.1	LGSQAGLKEIIAQNFPDKKVL	184	31-51	33	14	5	3	
SPO0737.1	DLAEAAAKTKALIIEDKTLTDDQRK	186	1436-1460	11	7	2		
SPO0737.2	TDDQRKEQLLGVDTEYAKGI	186	1455-1474	21	14	2	1	
SPO0737.3	EYAKGIENIDAAKDAAGVD	186	1469-1487	12	10	1		
SPO0747.1	VRDDSGKSIVVHIDH	187	215-229	29	11	9		
SPO0747.2	HLKPEKTNLQKDLSKLSIASYNIENFSA	187	534-561	14	12	1		



SPO0872.1	QAGIMVGASPANSALL	192	90-105	33	9	4	4	1
SPO0872.2	KVFNKMKFEYGTLGNHEFDEGLDEF	192	112-136	24	15	3	1	
SPO0895.1	FEKAVRNPLAHLIKPFDEEE	193	290-209	30	7	8	1	1
SPO0972.1	KGSRGSKKSKTTALNFTV	194	33-50	6	6			
SPO0981.1	DELQELKNDKTRNEL	195	76-90	12	12			
SPO1008.1	MLKYSVKDKNLSVFFEKDW	196	70-88	17	15	1		
SPO1032.1	TRIKTLVTQGNAFYNVYDNLKTYHD	197	418-442	17	11	3		
SPO1032.2	ASKKLNNTSALA	197	574-585	10	7		1	
SPO1054.1	EKGEQGPTGKQGERGETG	198	87-104	20	9	4	1	
SPO1054.2	VGPAGKDGQNGKDGLPGKDGKDGQN	198	124-148	15	13	1		
SPO1054.3	KDGKDGQNGKDG	198	141-152	3	3			
SPO1063.1	IKHAPNMT	199	241-248	41	5	3	10	
SPO1162.1	QSILKGDANSLSIAAA	200	183-198	19	14	1	1	
SPO1206.1	GLVGANGEGKSTFMSIVT	201	40-57	26	14	3	2	
SPO1228.1	GSFGDAAKGKTIAAAQ	202	202-217	14	14			
SPO1245.1	DEFGSSNLGKTVNVQGGGSGTGLSQ	203	50-74	5	5			
SPO1245.2	GTGLSQVQSGAVQIGNSDVFAEEKD	203	69-93	1	1			
SPO1245.3	FAEEKDGIDASKLVDHQVAVAGLAV	203	88-112	1	1			
SPO1245.4	VAGLAVIANPKVKVSNLSSQQ	203	107-127	5	3	1		
SPO1357.1	KKQAIEDKEATTAIEAASS	205	74-92	13	9	2		
SPO1361.1	PGLHFPTSDGFQFNGQGIVGVTKDSI	206	207-232	4	4			
SPO1361.2	VTKDSILVDHDGHLHPISFADLRQGG	206	227-252	6	6			
SPO1361.3	DLRQGGWAHVADQYDPAKKAEKPAET	206	247-272	9	7	1		
SPO1371.1	ASAKKALSDWRALS	207	47-60	5	5			
SPO1371.2	ADQLAAEIK	207	297-305	31	11	4	4	
SPO1371.3	SVGMPEDDADITPLIDTSAADFVEGL	207	312-337	2	2			
SPO1375.1	LYEWKTQSKQTTRDLSIL	208	667-384	25	13	3	2	
SPO1390.1	DKANVKIKDKAFANILA	210	279-295	25	15	2	2	
SPO1422.1	DIEYADEVTLLRAIENRTEL	211	179-198	17	15	1		
SPO1494.1	NHLSATGDKFDDCSTLVEKDVAPKD	213	27-51	8	8			
SPO1494.2	DVAPKDELEMLAWSSSQTTDDADRD	213	46-70	7	7			
SPO1494.3	DDADRDYEDFLDDDSFISQNETDKM	213	65-89	19	10	3	1	
SPO1494.4	NETDKMFENLTDDRLLNELDELDEE	213	84-108	14	10	2		
SPO1494.5	DEEDTIEPEQNVIMPSDDELFDLTDAVETR	213	112-141	27	12	3	3	
SPO1536.1	ITKEDLRKGRTIA	215	248-260	19	13	3		
SPO1564.1	IFVQANERIEDDFRSLEKRF	216	59-78	17	15	1		
SPO1607.1	AQKVSQKLFDKYQEKLP	218	154-170	28	15	5	1	
SPO1615.1	CRDCLKWENKGYNVNHR	219	57-73	15	11	2		
SPO1666.1	EDMKPKFELVSRKPILPS	220	297-314	37	11	5	4	1
SPO1727.1	KRSLPEFKSEVATIVH	221	142-157	26	14	3	2	
SPO1785.1	ELPAGRKPIMTRWVKHEQLG	222	428-447	20	14	3		
SPO1785.2	VLVANPKTDSGKKRMTIMTET	222	573-593	12	6		2	
SPO1798.1	EKVLVKLGKDLDGDGKLSKTEL	223	523-544	21	11	5		
SPO1798.2	RLLVEEIGPYASQSAGKEYYKHIEK	223	46-70	17	12	1	1	
SPO1798.3	YKHIEKIIVDNDVYEKSLEGERTFD	223	65-89	17	13	2		
SPO1798.4	GERTFDINYQGIKINADLIKDGKHE	223	84-108	18	12	3		
SPO1798.6	TFIKKGDKVTFISAQKLGTTDHQDSLKKDV	223	122-151	12	10	1		
SPO1801.1	KPTDQPKPSPSKVDTAPASS	224	123-142	2	2			
SPO1813.1	DTKGDRYSSPVVPELQILG	225	903-921	20	16	2		
SPO1821.1	EVIGVTVPTTVELTVAET	226	119-136	23	11	1	2	1
SPO1916.1	AEFCFKEFSEVNYWTTFNEI	227	142-161	12	10	1		
SPO1972.1	ANEIGFLILDKSKTGDAIKV	228	258-277	34	10	10		1
SPO1972.2	GDAIKVQPKDYLFKELDNHTQVFVKDTDP	228	272-300	27	12	6	1	
SPO1972.3	VKDTDPKVYNNPYYIDQVSLKGAEQTTP	228	295-322	18	16	1		
SPO1979.1	DPFDRSHLKLFTIKYVDVNTNELLKSEQLLTAS	229	311-343	15	12		1	
SPO1979.2	YEINPKTGIKEKINNTDLVSEKYYVLK	229	278-304	15	9	3		
SPO1983.1	ERGAQGPKGDRGEQGIQGKA	230	131-150	42	5	14	3	
SPO1983.2	PGEKGEKGDRGETGAQGPVGPQGE	230	195-218	24	16	4		
SPO1991.1	WPKEANQMPKLIQDFYQT	231	53-70	22	20	1		
SPO2000.1	NPIGSGPYMVKEYKAGEQAIFVRNP	232	184-208	20	16	2		
SPO2000.3	WVLLDENTALAALESGDVDMIYATP	232	222-246	11	11			
SPO2000.4	MIYATPELADKKVKGTRLLDIPSND	232	241-265	23	17	3		
SPO2000.5	DIPSNDVRGLSLPYVKKGVITDSPD	232	260-284	12	12			
SPO2000.6	ITDSPDGYPVGNDVTSDPAIRKALT	232	279-303	13	11	1		
SPO2000.8	NGYGKPAYSIIDKTPFWNPKTAIKD	232	317-341	26	14	6		
SPO2006.1	VLAKETFVWKDGSFSIPRA	233	678-696	23	9	7		
SPO2010.1	PAKTADTPATSKATIRDLNDPSQVKTL	235	88-114	30	11	3	3	1
SPO2010.2	PTASGTKLSRFSSWGLTA	235	464-481	45	6	7	7	1
SPO2016.1	KRDDWGGPGTVATDPYTPPY	236	153-172	51	6	6	7	3
SPO2016.2	DPYTPPYGGALGTGYEKRD	236	137-155, 166-184	22	8	4	2	
SPO2016.3	PQWNGFDGLSFGPS	236	215-228	46	5	12	3	2
SPO2018.1	TEVKANGDGNPREVI	237	37-51	18	14	2		
SPO2018.2	DLAANNPAIQNIRLRYENKDLKA	237	53-75	21	13	4		
SPO2018.3	EEEKQISDASRQSLRRDLDA	237	232-251	42	8	8	6	
SPO2018.4	EKQISDASRQGLRRDLDAS	237	318-336	17	11	3		
SPO2025.1	AFDENPNNAKK	238	305-315	27	16	4	1	
SPO2025.3	QNKDGRPTPSPDQQKTQTPDKTPEKS	238	131-156	8	5		1	
SPO2059.1	GNGVWGVEDASQKYFGIT	241	258-275	10	10			
SPO2127.1	ARAVAEMIDYTKTSQGYYDVQAMLRKVDEDE	243	107-137	12	10	1		

Table 2-2

Table 3: Gene distribution in *S. pyogenes* strains.

ORF	Common name	Gene distribution (present of 50)	Amino acid substitutions (in strain M89)	Homology (SP/EC)	Seq. ID (DNA, Prot.)
Spy0012	Hypothetical protein	50	3/302	SP0010 - 40%/None	1, 151
Spy0019	putative secreted protein (cell division and antibiotic tolerance)	50	0/300	SP2216 - 44-49%/None	2, 152
Spy0025	putative phosphoribosylformylglycinamidine synthase II	38	0/303	SP0045 - 85%/24%	3, 153
Spy0031	putative choline binding protein	50	0/297	SP2201 - 42% (cbpD)/None	4, 154
Spy0103	putative competence protein	50	0/81	SP2051 - 41%/None	5, 155
Spy0112	putative pyrroline carboxylate reductase	50	3/235	SP0933 - 32%/34%	6, 156
Spy0115	putative glutamyl-aminopeptidase	50	6/306	SP1865 - 76%/30%	7, 157
Spy0166	hypothetical protein	50	n.d.	None/None	8, 158
Spy0167	Streptolysin O	50	7/300	SP1923 - 40% (Pneumolysin)/None	9, 159
Spy0168	hypothetical protein	8	19/126	None/None	10, 160
Spy0171	hypothetical protein	18	8/95	None/None	11, 161
Spy0183	putative glycine betaine/proline ABC transporter	50	0/297	SP0151 - 39%/48%	12, 162
Spy0230	putative ABC transporter (ATP-binding protein)	50	1/299	SP2073 - 64%/32%	13, 163
Spy0269	putative surface exclusion protein	50	1/303	None/None	14, 164
Spy0287	conserved hypothetical protein	50	1/307	SP0868 - 71%/19%	15, 165
Spy0292	penicillin-binding protein (D-alanyl-D-alanine car	50	1/359	SP0872 – 47%/27%	16, 166
Spy0295	oligopeptidepermease	50	2/269	SP1889 - 69%/24%	17, 167
Spy0348	putative aminodeoxychorismate lyase	50	1/307	SP1518 - 47%/25%	18, 168
Spy0416	putative cell envelope serine proteinase	50	4/314	SP0641 - 22%/None	19, 169
Spy0430	hypothetical protein	13	0/165#	None/None	20, 170
Spy0433	hypothetical protein	21 (27/49)[1]	2/174#	None/None	21, 171
Spy0437	Hypothetical protein	19 (34/49)[1]	0/106#	None/None	22, 172
Spy0469	putative 42 kDa protein	50	6/313	SP2063 - 44% (LysM protein)/None	23, 173
Spy0488	hypothetical protein	50	9/178	None/None	24, 174
Spy0515	Putative sugar transferase	50	n.d.	SP1075– 26%/ None	25, 175
Spy0580	conserved hypothetical protein	50	0/297	SP0908 – 72%/43%	26, 176
Spy0621	conserved hypothetical protein	50	n.d.	SP1290 –72%/None	27, 177
Spy0630	putative PTS dependent N-acetyl-galactosamine-IIC	50	n.d.	SP0324 - 79%/30%	28, 178

Spy0681	hypothetical protein, phage associated	27	2/303#	None/None	29, 179
Spy0683	putative minor capsid protein, phage associated	25	1/233	None/None	30, 180
Spy0702	Hypothetical protein	22	n.d.	None/None	31, 181
Spy0710	conserved hypothetical protein, phage associated	32	51/286#	None/36% in 122 of 313aa	32, 182
Spy0711	pyrogenic exotoxin C precursor, phage associated (speC)	17	1/225	None/None	33, 183
Spy0720	conserved hypothetical protein	50	2/270	SP1298 - 60% (DHH 1 protein)/None	34, 184
Spy0727	Putative DNA gyrase, subunit B	n.d.	n.d.	SP0806- 80%/46%	35, 185
Spy0737	putative extracellular matrix binding protein	29 (48/49)[1]	0/466#	None/27% in 340of 421aa	36, 186
Spy0747	extracellular nuclease	50	0/179	None/None	37, 187
Spy0777	putative ATP-dependent exonuclease, subunit A	50	2/306	SP1152 - 48%/22%	38, 188
Spy0789	putative ABC-transporter (permease protein	50	1/231	None/None	39, 189
Spy0839	putative glycerophosphodiester phosphodieste	50	1/301	SP0994 - 24%/31% in 121 of 358aa	40, 190
Spy0843	cell surface protein	50	3/312	None/None	41, 191
Spy0872	putative secreted 5'-nucleotidase	50	2/309	None/27% in 274 of 647aa	42, 192
Spy0895	histidine protein kinase	50	0/244	None/None	43, 193
Spy0972	putative terminase, large subunit - phage	28	1/314#	None/None	44, 194
Spy0981	hypothetical protein - phage associated	23	n.d.	None/None	45, 195
Spy1008	streptococcal exotoxin H precursor (speH)	15 (14/49)[1]	1/223#	None/None	46, 196
Spy1032	extracellular hyaluronate lyase	50 (175 of 175, Hynes 2000)	3/311	SP0314 - 51%/None	47, 197
Spy1054	putative collagen-like protein (SclC)	26, (45/49)[1] (50 of 50, but varying number of repeats; Lukomski, 2001)	n.d.	None/None	48, 198
Spy1063	putative periplasmic-iron-binding protein	49/50 (49/49)[1]	2/292#	SP0243 - 52%, iron ABC transporter/26% in 161 of 348aa	49, 199
Spy1162	putative ribonuclease HII	50	3/240	SP1156 – 67%/46%	50, 200
Spy1206	putative ABC transporter	50	1/302	SP0770 - 81%/30%	51, 201
Spy1228	Putative lipoprotein	49	n.d.	SP0845-57%/None	52, 202
Spy1245	Putative ABC transporter	50	n.d.	SP1400-64%/None	53, 203
Spy1315	hypothetical protein	50	4/305	SP1241 - 64%/32%	54, 204
Spy1357	protein GRAB (protein G-related alpha 2M-binding protein)	49; 11 of 12 strains (Rasmussen, 1999)	9/226; insertion of 28 aa	None/None	55, 205
Spy1361	putative internalin A precursor	50	7/295	SP1004 – 26% in 283 of 1039/None	56, 206
Spy1371	putative NADP-dependent glyceraldehyde-3-phosphate dehydrogenase	50	2/308	SP1119 - 71%/34%	57, 207
Spy1375	putative ribonucleotide reductase alpha-c	50	4/304	SP1179 - 85%/49%	58, 208

Spy1389	putative alanyl-tRNA synthetase	50	0/309	SP1383 – 74%/40%	59, 209
Spy1390	putative protease maturation protein	50	0/232	SP0981 - 42%/None	60, 210
Spy1422	putative recombination protein	n.d.	n.d.	SP1672 - 88%/64%	61, 211
Spy1436	putative deoxyribonuclease	25	0/243#	SP1964 – 29% in 181 of 274aa/None	62, 212
Spy1494	hypothetical protein	50	13/282	None/None	63, 213
Spy1523	cell division protein	49	2/329	SP0690 – 27%/None	64, 214
Spy1536	conserved hypothetical protein	50	9/280	SP1967 - 57%/None	65, 215
Spy1564	conserved hypothetical protein	39	n.d.	None/None	66, 216
Spy1604	conserved hypothetical protein	50	1/233	SP2143 – 47%/28%	67, 217
Spy1607	conserved hypothetical protein	50	0/241	SP1902 - 55%/None	68, 218
Spy1615	putative late competence protein	50	2/204	SP2207 – 41%/None	69, 219
Spy1666	conserved hypothetical protein	50	2/305	SP0334 (yllC) - 78%/40%	70, 220
Spy1727	conserved hypothetical protein	50	0/237	SP0549 - 53%/None	71, 221
Spy1785	putative ATP-dependent DNA helicase	50	1/306	SP1697 - 71%/37%	72, 222
Spy1798	hypothetical protein	50	2/128	None/None	73, 223
Spy1801	immunogenic secreted protein precursor homolog	50	6/313; insertion of 6 aa	SP2216 – 33% in 119 of 392aa/None	74, 224
Spy1813	hypothetical protein	46	47/433; insertion of 9, deletion of 1 aa	None/None	75, 225
Spy1821	putative translation elongation factor EF-P	n.d.	n.d.	SP0435 - 94%/45%	76, 226
Spy1916	putative phospho-beta-D-galactosidase	n.d.	n.d.	SP1184 - 91%/83%	77, 227
Spy1972	Pullulanase	50	1/233	SP0268 - 53%, SP1118 - 29%/25% in 352 of 657aa	78, 228
Spy1979	streptokinase A precursor	50	20.1% identical of 309#	None/None	79, 229
Spy1983	collagen-like surface protein (SclD)	50, (50 of 50, but size variation according to Lukomski, 2000	n.d.	None/None	80, 230
Spy1991	anthranilate synthase component II	50	1/170	SP1816 – 58%/47%	81, 231
Spy2000	surface lipoprotein	50	0/307	None/27% in 389 of 524aa	82, 232
Spy2006	hypothetical protein	50	0/234	SP1003 - 36%, SP1174 - 37%, SP1004 - 33%, SP1175 - 48%/None	83, 233
Spy2009	hypothetical protein	39 (38/49) [1]	58/344; insertion of 36, deletion of 4 aa	None/None	84, 234
Spy2010	C5A peptidase precursor	n.d.	n.d.	SP0641 – 23% in 783 of 2140aa/None	85, 235
Spy2016	inhibitor of complement (Sic)	47; mainly in M1 strains (Reid 2001)	11/269#	None/None	86, 236
Spy2018	M1-Protein	n.d.	n.d.	None/None	87, 237
Spy2025	immunogenic secreted protein precursor	50	3/296	SP2216 – 31% in 138 of 392aa/None	88, 238
Spy2039	pyrogenic exotoxin B	n.d.	n.d.	None/None	89, 239

Spy2043	mitogenic factor MF1 (speF)	50	0/247	None/None	90, 240
Spy2059	penicillin-binding protein 2a	50	0/293	SP2010 - 55% (pbp2A)/30% in 539 of 844aa	91, 241
Spy2110	putative anaerobic ribonucleoside-triphosphate reductase	50	0/311	SP0202 - 80% (nrdD)/50%	92, 242
Spy2127	Hypothetical protein	1	n.d.	None/None	93, 243
Spy2191	hypothetical protein	50	1/175	None/None	94, 244
Spy2211	transmembrane protein	50	2/281	SP2231 - 43%/None	95, 245
ARF0450	hypothetical protein	50	5/191	None/None	96, 246
ARF0569	hypothetical protein	n.d.	n.d.	None/None	97, 247
ARF0694	hypothetical protein	23	1/122#	None/None	98, 248
ARF0700	hypothetical protein	n.d.	n.d.	None/None	99, 249
ARF1007	hypothetical protein	n.d.	n.d.	None/None	100, 250
ARF1145	hypothetical protein	n.d.	n.d.	None/None	101, 251
ARF1208	hypothetical protein	n.d.	n.d.	None/None	102, 252
ARF1262	hypothetical protein	n.d.	n.d.	None/None	103, 253
ARF1294	hypothetical protein	50	1/186	39% with SA0131 (first 28 aa of 67 aa protein)	104, 254
ARF1316	hypothetical protein	n.d.	n.d.	None/None	105, 255
ARF1352	hypothetical protein	n.d.	n.d.	38% with SA1142 (aa 265-295 of 358 protein)	106, 256
ARF1481	hypothetical protein	n.d.	n.d.	None/None	107, 257
ARF1557	hypothetical protein	n.d.	n.d.	None/None	108, 258
ARF1629	hypothetical protein	n.d.	n.d.	36% with SP0069 (aa 139-169 of 211 aa protein)	109, 259
ARF1654	hypothetical protein	n.d.	n.d.	None/None	110, 260
ARF2027	hypothetical protein	n.d.	n.d.	None/None	111, 261
ARF2093	hypothetical protein	n.d.	n.d.	None/None	112, 262
ARF2207	hypothetical protein	50	n.d.	38% with SP1006 (aa 7-37 of 67 aa protein)	113, 263
CRF0038	hypothetical protein	n.d.	n.d.	None/None	114, 264
CRF0122	hypothetical protein	n.d.	n.d.	None/None	115, 265
CRF0406	hypothetical protein	n.d.	n.d.	None/None	116, 266
CRF0416	hypothetical protein	n.d.	n.d.	None/None	117, 267
CRF0507	hypothetical protein	n.d.	n.d.	None/None	118, 268
CRF0549	hypothetical protein	n.d.	n.d.	None/None	119, 269
CRF0569	hypothetical protein	n.d.	n.d.	None/None	120, 270
CRF0628	hypothetical protein	n.d.	n.d.	None/None	121, 271
CRF0727	hypothetical protein	n.d.	n.d.	40% with SP0584 (aa21-60 of 70aa protein)	122, 272
CRF0742	hypothetical protein	n.d.	n.d.	33% with SA0422 (aa 11-37 of 42 aa protein, listed as 280 aa protein)	123, 273
CRF0784	hypothetical protein	n.d.	n.d.	None/None	124, 274

CRF0854	hypothetical protein	n.d.	n.d.	None/None	125, 275
CRF0875	hypothetical protein	n.d.	n.d.	None/None	126, 276
CRF0907	hypothetical protein	n.d.	n.d.	Homology to lysosomal trafficking regulator LYST [Homo sapiens]	127, 277
CRF0979	hypothetical protein	n.d.	n.d.	None/None	128, 278
CRF1068	hypothetical protein	50	0/148	None/None	129, 279
CRF1152	hypothetical protein	n.d.	n.d.	None/None	130, 280
CRF1203	hypothetical protein	n.d.	n.d.	None/None	131, 281
CRF1225	hypothetical protein	n.d.	n.d.	None/None	132, 282
CRF1236	hypothetical protein	n.d.	n.d.	None/None	133, 283
CRF1362	hypothetical protein	n.d.	n.d.	None/None	134, 284
CRF1524	hypothetical protein	n.d.	n.d.	None/None	135, 285
CRF1525	hypothetical protein	n.d.	n.d.	None/None	136, 286
CRF1527	hypothetical protein	n.d.	n.d.	None/None	137, 287
CRF1588	hypothetical protein	n.d.	n.d.	None/None	138, 288
CRF1649	hypothetical protein	n.d.	n.d.	None/None	139, 289
CRF1749	hypothetical protein	n.d.	n.d.	None/None	140, 290
CRF1903	hypothetical protein	50	0/140	None/None	141, 291
CRF1964	hypothetical protein	n.d.	n.d.	None/None	142, 292
CRF2055	hypothetical protein	n.d.	n.d.	None/None	143, 293
CRF2091	hypothetical protein	n.d.	n.d.	None/None	144, 294
CRF2096	hypothetical protein	n.d.	n.d.	None/None	145, 295
CRF2104	hypothetical protein	n.d.	n.d.	None/None	146, 296
CRF2116	hypothetical protein	n.d.	n.d.	None/None	147, 297
CRF2153	hypothetical protein	n.d.	n.d.	None/None	148, 298
NRF0001	hypothetical protein	50	0/130	ARF in Oligo ABC transporter (not annotated by TIGR), 33% with SA0643 (aa 107-162 of 469 aa protein)	149, 299
NRF0003	hypothetical protein	n.d.	n.d.	None/None	150, 300

Table 4: Recombinant proteins used for immunisation experiments in NMRI mice.

ORF	Length (amino acids)	Amino acids[A]		Solubility	Protection[B]	Total size of the fragment cloned (Kbp)
		From	to			
Spy0031	374	39	374	Insoluble	20 % (10 %, 40 %)	1.008
Spy0103	108	2	108		*50% (10%, 80%)*	0.321
Spy 0269	873	36	873	Soluble	40% (40%, 70%)[C]	2.511
Spy 0292	***410***	22	410	***Insoluble***	70% (10%, 80%)	1.164
Spy0416A	***1647***	33	867	***Soluble***	50 % (10 %, 40 %)	2.502
Spy0416B	1647	736	1617	Solubilized	0 % (0%, 40 %)	2.646
Spy0720	***313***	2	313	***Insoluble***	60% (10%, 80%)	0.939
Spy0872	***670***	27	640	Solubilized	60% (10%, 80%)	1.839
Spy1245	288	49	288	Soluble	20 % (10 %, 40 %)	0.717
Spy1357	217	33	186	Soluble	40 % (30%, 90 %)	0.459
Spy1361	792	22	792	Soluble	60 % (30%, 90 %)	2.31
Spy1390	***351***	21	351		60% (10%, 80%)	0.99
Spy1536	345	31	345		20 % (0%, 40 %)	0.942
Spy1607	258	2	258		40 % (10 %, 40 %)	0.771
Spy1666	337	22	337	Soluble	50 % (30%, 90 %)	0.945
Spy1972	1165	45	500		40 % (30%, 90 %)	1.365
Spy2000	542	24	542	Soluble	20 % (30%, 90 %)	1.554
Spy2025	541	27	541		40 % (40%, 70%)	1.542
Spy2191	204	36	204		50% (10%, 80%)	0.504

Table 5: Variability of antigens in strains of *S. pyogenes*.

Antigen name	Seq ID	Residue in Antigen[A]	Residue number	Amino acid variations[B]
Spy0031	154	G	126	D
		A	192	S
		V	233	I
		D	328	N
		I	338	T
Spy0103	155	none		
Spy0269	164	H	97	N
		A	150	V
		A	168	V
		H	482	R
		N	485	K
		Q	577	E
		A	610	V
		L	636	M
		E	640	K
		P	752	S
		I	764	V
		D	765	E
		K	873	R
Spy0292	166	A	214	D
		Y	309	S
		T	317	N
		V	318	C
		K	319	Q
Spy0416	169	V	1	M
		F	25	M
		L	26	M
		V	27	M
		S	38	T
		M	40	T
		A	49	T
		S	68	P
		L	76	P
		S	85	P
		D	87	G
		S	104	P
		S	110	P
		D	151[C]	A, S, T, G
		S	164	P
		E	215	G
		H	279[C]	A, S, T, G
		T	395	I
		D	452	N
		N	478	K
		G	484	D
		A	547	V
		S	617[C]	A, S, T, G

		D	723	A
		H	749	R
		R	770	K
		P	787	S
		D	804	A
		T	874	M
		N	913	S
		H	991	Y
		N	1080	S
		V	1238	A
		D	1313	G
		V	1349	M
		A	1393	V
		N	1479	K
		I	1487	M
		D	1516	G
		N	1555	D
		T	1560	A
		S	1599	F
		S	1605	T
		T	1617	A
Spy0720	184	A	61	T
		I	63	M
		K	99	Q
		K	109	Q
		N	295	S
Spy0872	192	K	178	N
		P	181	S
		V	253	I
		A	393	V
		T	600	I
		V	605	I
Spy1063	199	N	168	S
		A	169	S
		D	170	E
		A	173	E
		M	175	V
		V	180	L
		N	181	S
		E	192	D
		Q	195	E
		K	228	D
		H	243	K
		P	245	K
		N	246	A
		T	248	K
		L	252	Q
		M	257	I
		R	260	S
		Q	277	R
		D	284	E
		A	287	P
		E	289	D

		T	290	E
		A	292	I
		A	299	G
		K	303	R
		V	309	L
		A	310	N
		Q	314	R
		R	316	H
		Q	317	E
		R	318	A
		K	321	R
		A	322	G
Spy1245	203	L	72	M
		A	97	P
		Q	213	K
Spy1357	205	C	9	Y
		G	48	R
		I	87	L
		S	91	A
		T	102	A
		L	105	V
		A	111	S
		N	117	T
		E	139	S, A
		Q	142	K
		S	143	A
		N	145	T
		W	151	L
		A	155	D
		T	156	N
		P	157	A
		I	158	T, A
		A	159	S
		L	160	D
		D	161	A
		V	162	L
		K	163	E
		K	164	A
		T	165	L
		K	166	A
		T	168	Q
		K	169	T
		P	170	S, D
		V	171	A
		K	173	Q
		K	174	S
		G	187	S
		A	197	T
		V	207	A
Spy1361	206	R	129	Q
		P	141	S
		L	197	P
		A	201	V

		D	230	A
		S	231	N
		D	235	N
		P	262	L
		T	272	N
		Q	274	H
		T	302	A
		T	308	I
		A	346	V
		V	354	F
		P	389	L
		M	391	K
		I	427	L
		P	431	L
		P	503	S
		D	645	N
		S	696	P
		K	738	N
		T	757	A
Spy1390	210	N	3	Q
		S	4	M
		A	9	T
		S	10	G
		S	16	T
		M	18	V
		A	19	T
		A	21	S
		T	26	S
		N	27	H
		D	28	N
		V	32	L
		I	33	V
		S	41	T
		V	54	L
		S	55	A
		N	61	S
		A	70	T
		G	73	A
		D	74	N
		K	78	D
		H	86	K
		K	87	Q
		E	90	D
		A	94	T
		S	97	K
		A	98	T
		A	99	V
		S	104	G
		F	110	Y
		R	112	K
		S	116	L
		S	117	T
		A	127	Q

K	130	N
L	132	I
T	133	S
T	134	K
Q	135	K
E	136	D
K	138	R
K	139	Q
E	142	D
S	143	A
A	149	T
V	150	A
M	152	I
I	153	M
T	154	Q
L	155	F
D	156	E
N	157	K
E	158	D
T	160	D
S	163	A
V	164	A
T	176	A
T	184	I
T	185	A
P	186	A
E	187	D
V	190	T
K	193	T
A	198	E
T	199	I
N	200	T
V	201	L
T	203	A
D	204	E
K	207	R
S	211	G
N	213	K
G	216	N
I	217	R
D	219	E
V	220	I
S	222	T
V	223	A
T	227	A
S	228	T
Y	229	S
Q	230	K
K	231	R
K	232	T
F	233	Y
Y	234	H
V	236	I

		E	243	T
		S	246	A
		Q	249	K
		E	250	A
		E	252	A
		A	257	D
		I	260	V
		A	261	T
		E	262	G
		S	264	L
		M	267	P
		N	268	D
		N	276	K
		Y	297	F
		N	299	K
		L	300	P
		G	301	N
		T	304	Q
		K	305	P
		A	307	Q
		S	308	K
Spy1536	215	none		
Spy1607	218	E	21	D
		A	91	P
		H	194	R
		D	204	G, N
Spy1666	220	K	90	Q
		K	302	T
			S. peumoniae TIGR4	
		V	37	I
		I	42	V
		S	56	A
		A	60	E
		G	67	S
		E	69	K
		C	74	A
		K	80	N
		V	87	K
		T	88	R
		K	90	A,Q
		S	91	P
		D	94	E
		Q	97	M
		K	109	Q
		R	111	C
		T	113	R
		A	114	E
		L	115	A
		D	118	Q
		L	124	C
		E	136	Q
		Q	145	K
		D	154	N

		R	155	Q
		Q	156	D
		S	157	A
		L	158	S
		T	167	N
		P	169	D
		F	170	Y
		N	171	H
		K	175	R
		A	198	E
		I	199	V
		L	211	I
		A	214	L
		A	215	V
		D	252	Q
		E	255	D
		L	256	M
		D	287	E
		L	294	F
		E	297	D
		M	299	L
		F	303	M
		H	315	A
		S	316	E
		T	319	E
		K	322	N
		A	324	S
		A	332	V
		K	333	R
		R	336	H
Spy1972	228	V	32	M
		L	70	F
		M	98	I
		K	182	R
		F	224	S
		D	226	E
		H	245	P
		P	300	L
		R	363	K
		K	365	T
		T	369	A
		A	376	T
		R	443	K
		V	445	L
		A	460	T
		V	467	I
		D	510	V
		A	496	T
		T	611	K
		T	718	A
		G	831	S
		A	913	V
		Q	930	K

		V	1053	A
		E	1079	D
		N	1094	D
		T	1102	I
		D	1103	G
		I	1149	V
Spy2000	232	K	27	N
		S	101	L
		V	151	I
		D	250	S
		P	335	S
		A	338	P
		V	519	I
Spy2025	238	S	33	N
		D	46	A
		D	49	A
		P	54	A
		T	78	N
		D	107	N
		K	109	N
		D	112	N
		P	119	S
		Q	147	P
		T	160	I
		D	170	E
		I	183	N
		I	194	A
		G	297	E
		S	528	R
Spy2191	244	A	70	V
		V	93	A

Claims:

1. An isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence which is selected from the group consisting of:
   a) a nucleic acid molecule having at least 70% sequence identity to a nucleic acid molecule selected from **Seq ID No** 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150.,
   b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
   c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
   d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b), or c)
   e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid molecule defined in a), b), c) or d).

2. The isolated nucleic acid molecule according to claim 1, wherein the sequence identity is at least 80%, preferably at least 95%, especially 100%.

3. An isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence selected from the group consisting of
   a) a nucleic acid molecule having at least 96% sequence identity to a nucleic acid molecule selected from **Seq ID No** 64.
   b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
   c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
   d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b) or c),
   e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).

4. An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of
   a) a nucleic acid molecule selected from **Seq ID No** 3, 36, 47-48, 55, 62, 72, 80, 84, 95,
   b) a nucleic acid molecule which is complementary to the nucleic acid of a),
   c) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).

5. The nucleic acid molecule according to any one of the claims 1, 2, 3 or 4, wherein the nucleic acid is DNA.

6. The nucleic acid molecule according to any one of the claims 1,2, 3, 4, or 5 wherein the nucleic acid is RNA.

7. An isolated nucleic acid molecule according to any one of claims 1 to 5, wherein the nucleic acid molecule is isolated from a genomic DNA, especially from a S. pyogenes genomic DNA.

8. A vector comprising a nucleic acid molecule according to any one of claims 1 to 7.

9. A vector according to claim 8, wherein the vector is adapted for recombinant expression of the hyperimmune serum reactive antigens or fragment thereof encoded by the nucleic acid molecule according to any one of claims 1 to 7.

10. A host cell comprising the vector according to claim 8 or 9.

11. A hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to any one of the claims 1, 2, 5, 6 or 7 and fragments thereof, wherein the amino acid sequence is selected from the group consisting of **Seq ID No** 151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244 and 246-300.

12. A hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to any one of the claims 3, 5, 6, or 7 and fragments thereof, wherein the amino acid sueqnece is selected from the group consisting of **Seq ID No** 214.

13. A hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to any one of the claims 4, 5, 6, or 7 and fragments thereof, wherein the amino acid sequence is selected from the group consisting of **Seq ID No** 153, 186, 197-198, 205, 212, 222, 230, 234, 245.

14. Fragments of hyperimmune serum-reactive antigens selected from the group consisting of peptides comprising amino acid sequences of column "predicted immunogenic aa" and "location of identified immunogenic region" of Table 2; the serum reactive epitopes of Table 2, especially peptides comprising amino acid 4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425 and 1-114 of **Seq ID No** 151; 5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395 and 29-226 of **Seq ID No** 152; 4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254 and 919-929 of **Seq ID No** 153; 5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360 and 145-305 of **Seq ID No** 154; 15-39, 52-61, 72-81, 92-97 and 71-81 of **Seq ID No** 155; 13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245 and 173-186 of **Seq ID No** 156; 5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352 and 316-331 of **Seq ID No** 157; 6-28, 43-53, 60-76, 93-103 and 21-99 of **Seq ID No** 158; 10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568 and 9-264 of **Seq ID No** 159; 5-29, 39-45, 107-128 and 1-112 of **Seq ID No** 160; 4-38, 42-50, 54-60, 65-71, 91-102 and 21-56 of **Seq ID No** 161; 4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391 and 23-39 of **Seq ID No** 162; 6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591 and 474-489 of **Seq ID No** 163; 8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864 and 37-241, 409-534, 582-604, 743-804 of **Seq ID No** 164; 4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416 and 202-337 of **Seq ID No** 165; 4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407 and 1-48 of **Seq ID No** 166; 18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-

207, 212-229, 232-253, 273-297 and 203-217 of **Seq ID No** 167; 20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521 and 261-273 of **Seq ID No** 168; 6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641 and 1-414, 443-614, 997-1392 of **Seq ID No** 169; 14-42, 70-75, 90-100, 158-181 and 1-164 of **Seq ID No** 170; 4-21, 30-36, 54-82, 89-97, 105-118, 138-147 and 126-207 of **Seq ID No** 171; 4-21, 31-66, 96-104, 106-113, 131-142 and 180-204 of **Seq ID No** 172; 5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386 and 11-197, 204-219, 258-372 of **Seq ID No** 173; 4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322 and 195-289 of **Seq ID No** 174; 4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329 and 12-130 of **Seq ID No** 175; 10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707 and 434-444 of **Seq ID No** 176; 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15. A process for producing a S. pyogenes hyperimmune serum reactive antigen or a fragment thereof according to any one of the claims 11 to 14 comprising expressing the nucleic acid molecule according to any one of claims 1 to 7.

16. A process for producing a cell, which expresses a S. pyogenes hyperimmune serum reactive antigen or a fragment thereof according to any one of the claims 11 to 14 comprising transforming or transfecting a suitable host cell with the vector according to claim 8 or claim 9.

17. A pharmaceutical composition, especially a vaccine, comprising a hyperimmune serum-reactive antigen or a fragment thereof, as defined in any one of claims 11 to 14 or a nucleic acid molecule according to any one of claims 1 to 7.

18. A pharmaceutical composition, especially a vaccine, according to claim 17, characterized in that it further comprises an immunostimulatory substance, preferably selected from the group comprising polycationic polymers, especially polycationic peptides, immunostimulatory deoxynucleotides (ODNs), peptides containing at least two LysLeuLys motifs, neuroactive compounds, especially human growth hormone, alumn, Freund's complete or incomplete

adjuvants or combinations thereof.

19. Use of a nucleic acid molecule according to any one of claims 1 to 7 or a hyperimmune serum-reactive antigen or fragment thereof according to any one of claims 11 to 14 for the manufacture of a pharmaceutical preparation, especially for the manufacture of a vaccine against S. pyogenes infection.

20. An antibody, or at least an effective part thereof, which binds at least to a selective part of the hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14.

21. An antibody according to claim 20, wherein the antibody is a monoclonal antibody.

22. An antibody according to claim 20 or 21, wherein said effective part comprises Fab fragments.

23. An antibody according to any one of claims 20 to 22, wherein the antibody is a chimeric antibody.

24. An antibody according to any one of claims 20 to 23, wherein the antibody is a humanized antibody.

25. A hybridoma cell line, which produces an antibody according to any one of claims 20 to 24.

26. A method for producing an antibody according to claim 20, characterized by the following steps:
- initiating an immune response in a non-human animal by administrating an hyperimmune serum-reactive antigen or a fragment thereof, as defined in any one of the claims 11 to 14, to said animal,
- removing an antibody containing body fluid from said animal, and
- producing the antibody by subjecting said antibody containing body fluid to further purification steps.

27. Method for producing an antibody according to claim 21, characterized by the following steps:
- initiating an immune response in a non-human animal by administrating an hyperimmune serum-reactive antigen or a fragment thereof, as defined in any one of the claims 12 to 15, to said animal,
- removing the spleen or spleen cells from said animal,
- producing hybridoma cells of said spleen or spleen cells,
- selecting and cloning hybridoma cells specific for said hyperimmune serum-reactive antigens or a fragment thereof,
- producing the antibody by cultivation of said cloned hybridoma cells and optionally further purification steps.

28. Use of the antibodies according to any one of claims 20 to 24 for the preparation of a medicament for treating or preventing S. pyogenes infections.

29. An antagonist which binds to the hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14.

30. A method for identifying an antagonist capable of binding to the hyperimmune serum-reactive antigen or fragment thereof according to any one of claims 11 to 14 comprising:
   a) contacting an isolated or immobilized hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14 with a candidate antagonist under conditions to permit binding of said candidate antagonist to said hyperimmune serum-reactive antigen or

fragment, in the presence of a component capable of providing a detectable signal in response to the binding of the candidate antagonist to said hyperimmune serum reactive antigen or fragment thereof; and

b) detecting the presence or absence of a signal generated in response to the binding of the antagonist to the hyperimmune serum reactive antigen or the fragment thereof.

31. A method for identifying an antagonist capable of reducing or inhibiting the interaction activity of a hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14 to its interaction partner comprising:

a) providing a hyperimmune serum reactive antigen or a hyperimmune fragment thereof according to any one of claims 11-14,
b) providing an interaction partner to said hyperimmune serum reactive antigen or a fragment thereof, especially an antibody according to any one of the claims 20 to 24,
c) allowing interaction of said hyperimmune serum reactive antigen or fragment thereof to said interaction partner to form a interaction complex,
d) providing a candidate antagonist,
e) allowing a competition reaction to occur between the candidate antagonist and the interaction complex ,
f) determining whether the candidate antagonist inhibits or reduces the interaction activities of the hyperimmune serum reactive antigen or the fragment thereof with the interaction partner.

32. Use of any of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11 to 14 for the isolation and/or purification and/or identification of an interaction partner of said hyperimmune serum reactive antigen or fragment thereof.

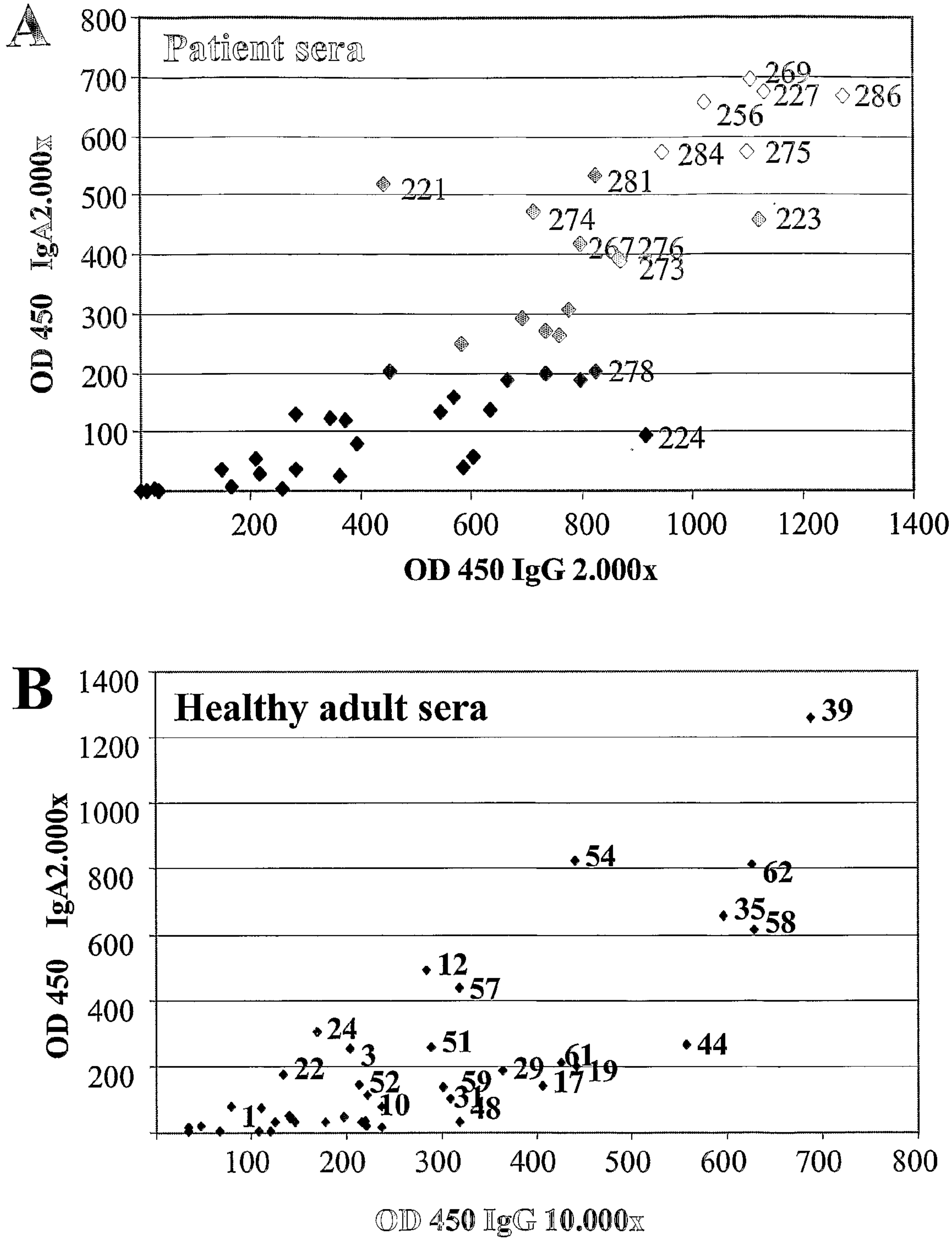
33. A process for *in vitro* diagnosing a disease related to expression of the hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14 comprising determining the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to any one of claims 1 to 7 or the presence of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11-14.

34. A process for *in vitro* diagnosis of a bacterial infection, especially a S. pyogenes infection, comprising analysing for the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to any one of claims 1 to 7 or the presence of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11 to 14.

35. Use of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11 to 14 for the generation of a peptide binding to said hyperimmune serum reactive antigen or fragment thereof, wherein the peptide is selected from the group comprising anticalines.

36. Use of the hyperimmune serum-reactive antigen or fragment thereof according to any one of claims 11 to 14 for the manufacture of a functional nucleic acid, wherein the functional nucleic acid is selected from the group comprising aptamers and spiegelmers.

37. Use of a nucleic acid molecule according to any one of claims 11 to 14 for the manufacture of a functional ribonucleic acid, wherein the functional ribonucleic acid is selected from the group comprising ribozymes, antisense nucleic acids and siRNA.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600
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1200
1400
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256
284
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281
274
223
267
276
273
278
224
B
Healthy adult sera
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OD 450 IgG 10.000x
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300
400
500
600
700
800
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62
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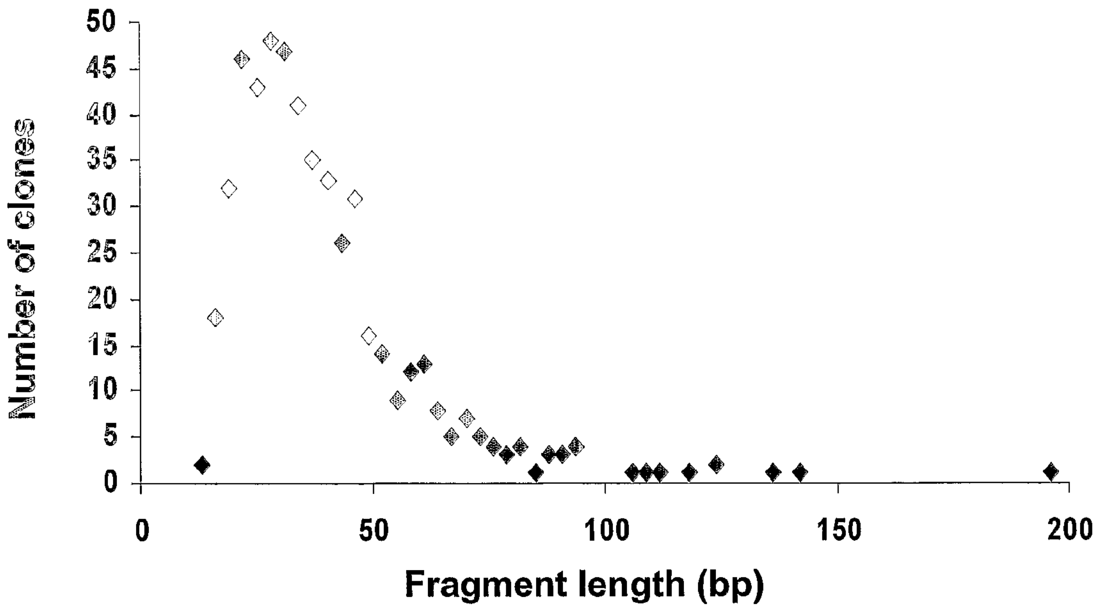
10
48
1

Figure 1

A



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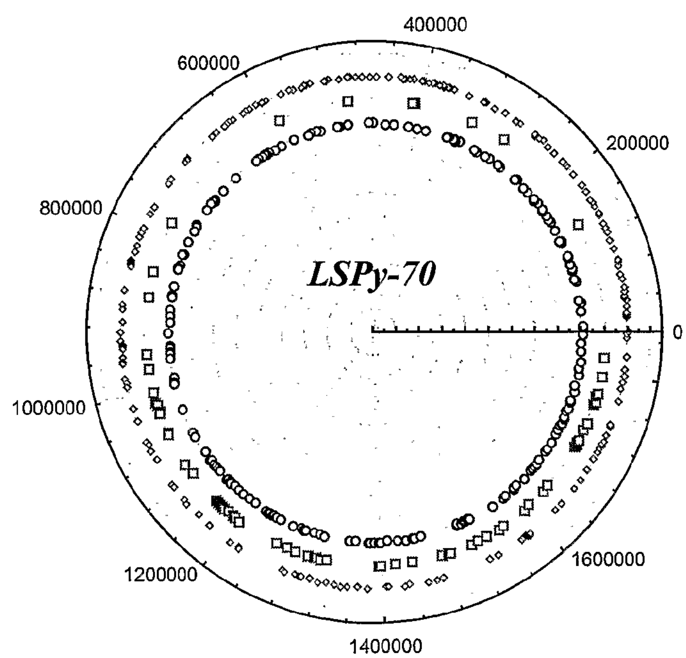
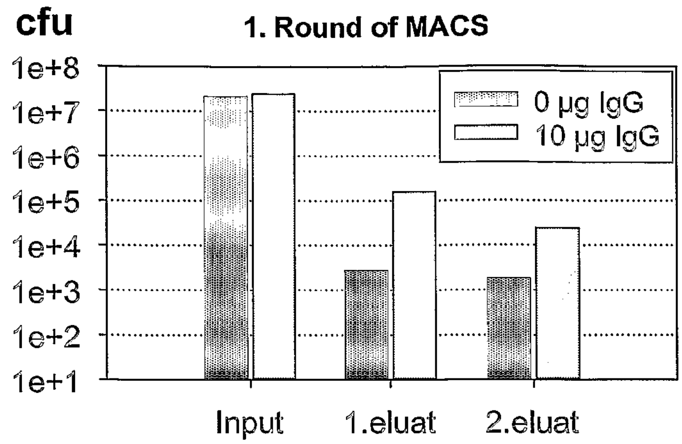


Total (trimmed)		505	(100.0 %)
ORF (+/+)	○	211	(42.0 %)
Non-ORF (+/+)	□	74	(14.6 %)
Other (contig +/-)	◇	83	(16.4 %)
Other (chimeric)	◇	136	(27.0 %)

Figure 2

A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1e+7
1e+6
1e+5
1e+4
1e+3
1e+2
1e+1
0 µg IgG
10 µg IgG
Input
1.eluat
2.eluat
cfu
2. Round of MACS
1e+8
1e+7
1e+6
1e+5
1e+4
1e+3
1e+2
1e+1
0 µg IgG
10 µg IgG
Input
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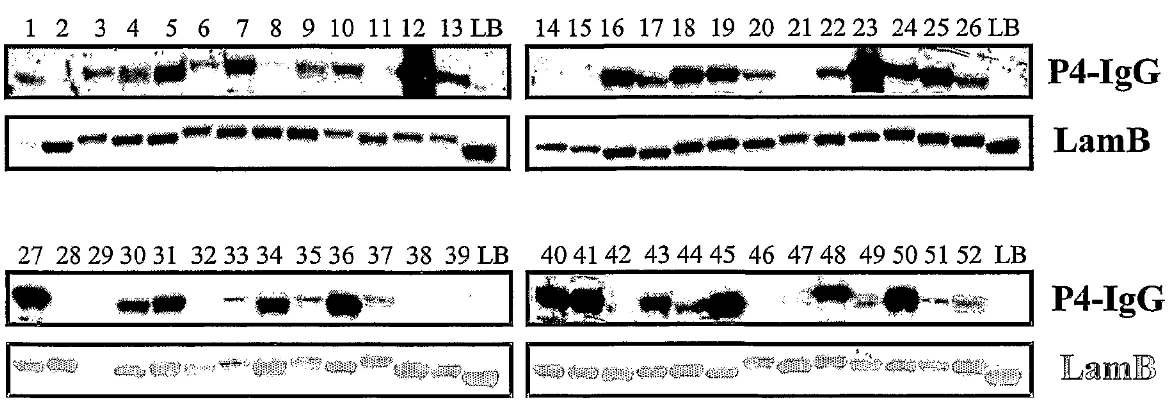
2.eluat

Figure 3

B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14 15 16 17 18 19 20 21 22 23 24 25 26 LB
P4-IgG
LamB
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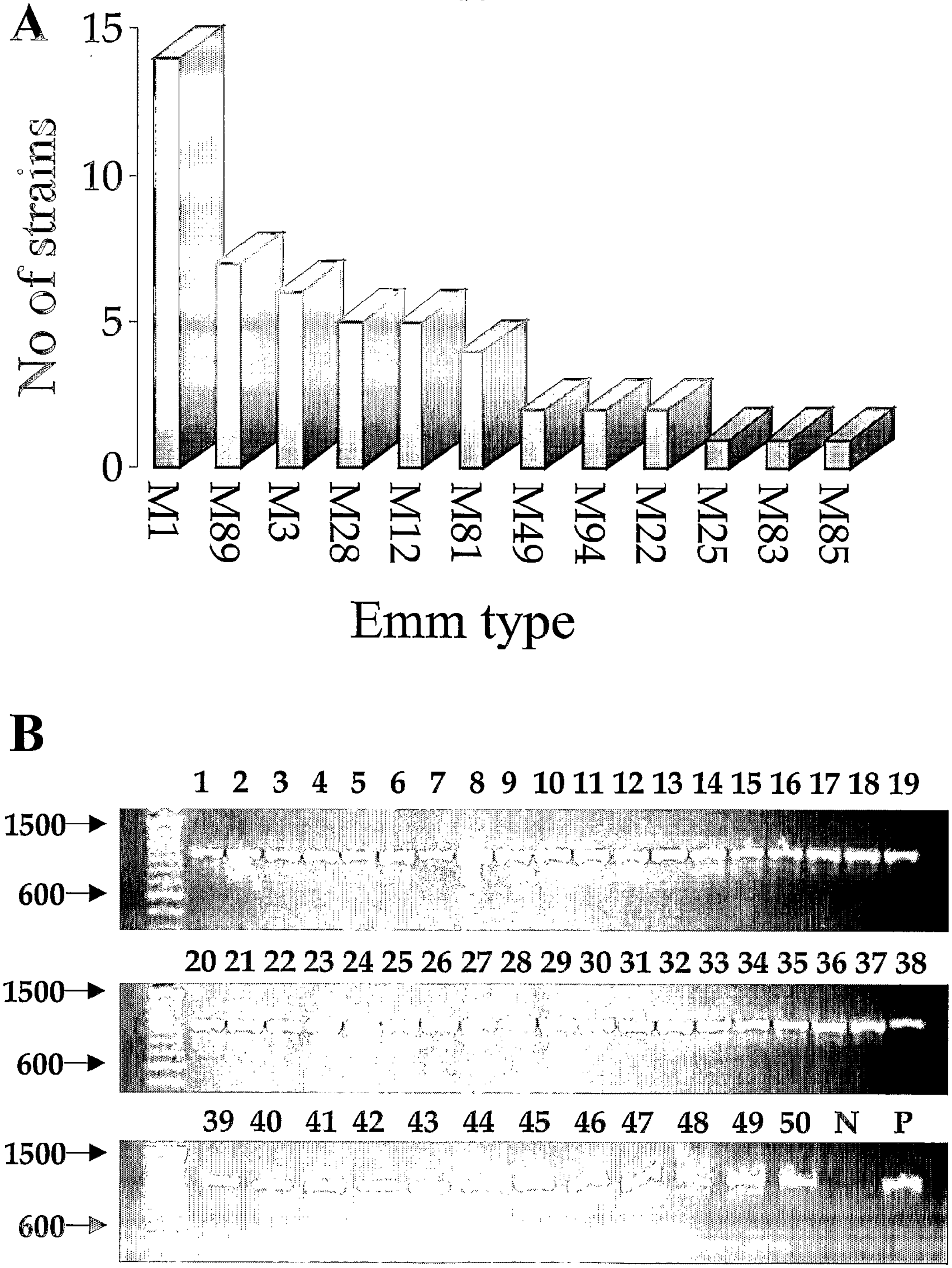
P4-IgG
LamB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M89
M3
M28
M12
M81
M49
M94
M22
M25
M83
M85
Emm type
B
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
1500
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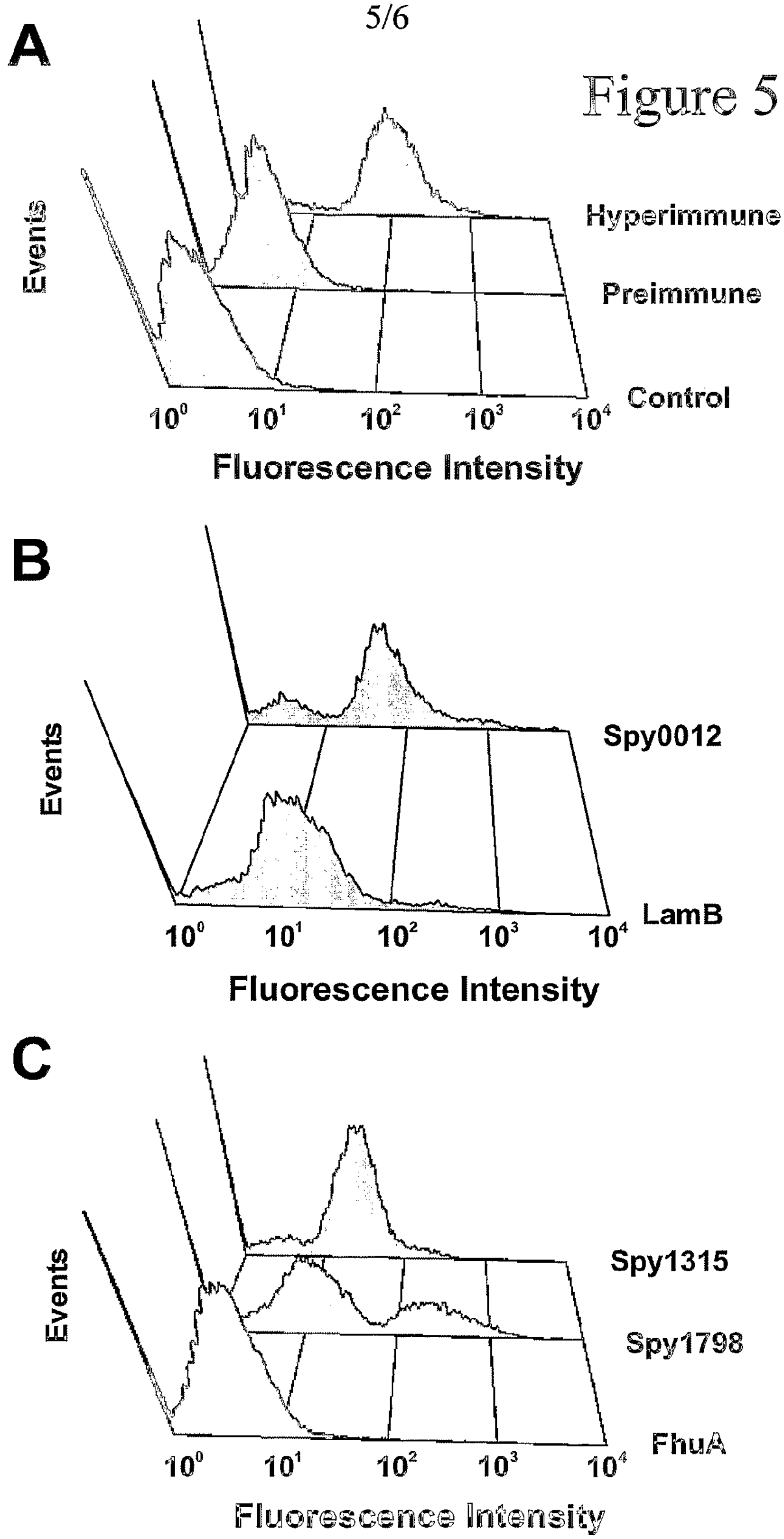
Figure 4

Figure 5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Hyperimmune
Preimmune
Control
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Spy0012
LamB
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Fluorescence Intensity
C
Events
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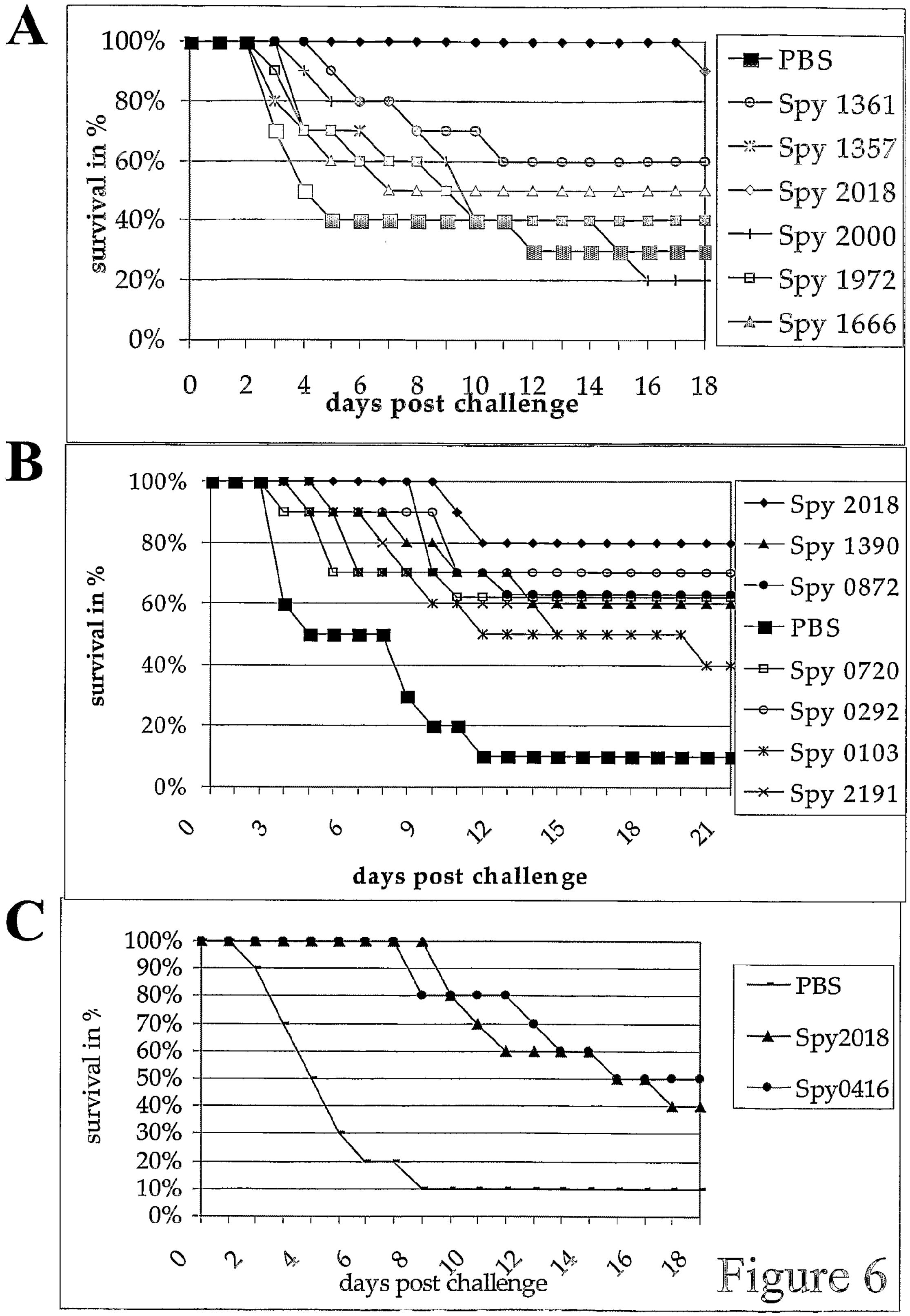
Spy1798
FhuA
10^0 10^1 10^2 10^3 10^4
Fluorescence Intensity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80%
60%
40%
20%
0%
survival in %
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days post challenge
PBS
Spy 1361
Spy 1357
Spy 2018
Spy 2000
Spy 1972
Spy 1666
B
100%
80%
60%
40%
20%
0%
survival in %
0 3 6 9 12 15 18 21
days post challenge
Spy 2018
Spy 1390
Spy 0872
PBS
Spy 0720
Spy 0292
Spy 0103
Spy 2191
C
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
survival in %
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days post challenge
PBS
Spy2018
Spy0416

Figure 6

Sequence Listing

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SPy0031
Seq ID 4
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SPy0103
Seq ID 5
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SPy0112
Seq ID 6
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AAAGCTTGTAA

SPy0115
Seq ID 7
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SPy0166
Seq ID 8
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SPy0167
Seq ID 9
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SPy0168
Seq ID 10
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SPy0171
Seq ID 11
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SPy0183
Seq ID 12
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SPy0230
Seq ID 13
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SPy0269
Seq ID 14
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SPy0287
Seq ID 15
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SPy0292
Seq ID 16
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SPy0295
Seq ID 17
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SPy0348
Seq ID 18
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SPy0416
Seq ID 19
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SPy0430
Seq ID 20
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GGAGAAGGACAACATAAACGTGATCCATTAGAAACAGAAGCAGAAGATGATTCTCAAGGAGGACGTCAAGAAGGACGTCAAGG
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SPy0433
Seq ID 21
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SPy0437
Seq ID 22
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SPy0469
Seq ID 23
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SPy0488
Seq ID 24
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SPy0515
Seq ID 25
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SPy0580
Seq ID 26
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SPy0621
Seq ID 27
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AATGGGCATTTTCACTTTAGTCAGTAA

SPy0630
Seq ID 28
ATGGATATCAATTTGTTACAGGCACTTTTAATTGGTCTTTGGACAGCCTTTTTGTTTCAGCGGAATGTTACTTGGCATCTACACCAA
CCGTTGTATTATTCTGTCTTTTGGTGTAGGGATTATCTTAGGTGACTTGCCAACTGCACTTAGCATGGGAGCTATCTCCGAATTA
GCTTATATGGGATTTGGAGTGGGTGCCGGTGGTACCGTTCCTCCTAATCCTATCGGCCCTGGTATCTTTGGTACCTTGATGGCT
ATTACCAGTGCTGGTAAAGTCACCCCAGAAGCGGCACTAGCCTTATCAACACCAATCGCAGTTGCCATCCAATTCCTTCAAACA

TTCGCCTATACAGCTTTTGCTGGCGCTCCCGAAACCGCTAAAAAACAATTGCAAAAAGGCAATATTAGAGGCTTCAAATTCGCTG
CCAACGGCACTATCTGGGCTTTCGCTTTTATCGGATTAGGCCTTGGTTTATTAGGTGCCTTGTCAATGGATACTCTCCTTCACTT
GGTTGATTATATCCCACCTGTCTTGCTCAATGGATTGACTGTCGCTGGTAAAATGTTACCTGCTATCGGATTTGCCATGATCTTA
TCTGTTATGGCCAAGAAAGAATTGATTCCTTTTGTACTAATTGGTTATGTTTGTGCAGCCTACCTCCAAATTCCAACCATTGGTAT
CGCCATTATTGGTATCATTTTCGCCTTGAATGAATTTTACAACAAACCTAAACAAGTCGATGCAACAACTGTCCAAGGAGGCCAA
CAAGATGACTGGATCTAA

SPy0681
Seq ID 29
TTGACCCCTCGTAGCGGAAAGACCACAGCTGGGCATTTTCGTTATGCTAGGTATCTGATTGAGTCAGAAGATGAAAATCACCTT
GTGACTGCTTATAATCAAGAACAAGCTTATCGTTTGTTTATCGACGGCGATGGTACGGGTTTGATGCATATATTTGACGGTAACT
GTGAAATAAAACACGACGAGCGTGGAGATCACTTGTTAATCACGACACCAAAAGGCAATAAGCGCGTTTATTATAAAGGCGGCG
GTAAAGTTAACAGTGTTGGTGCTATTACAGGTATGTCTTTAGGATCAGTAGTATTCTGCGAGATTAACTTACTGCACATGGATTTT
ATCCAGGAGTGTTTTAGGCGTACTTGGGCGGCTAAGCTACGTTATCATCTAGCAGATTTAAATCCCCCAGCACCTCAACATCCA
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ACTGGTGCGTTAAAAAGTATCAGATGCGCTATACAGAGGTATTTGTGGATCCTGCCTGTAAATCTTTGAGAGAGGAGCTGCATA
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GCGGCCAAAACATTATCTCAGATGGCGCTTTTTATCTTGTTAATCATAGCGAAGAAGAGTATGACCACTACCACTTTTTAAAAGA
GATAGGGCTGTACAGTCGTGACGACAATGGCAAACCTATTGATAAAGATAACCATGCCATGGACGAGTTTAGATACAGCGTCAA
CGTGTTTGTGCATCGGTATTACAACTAA

SPy0683
Seq ID 30
ATGAAAAAGAAGCCTATTAAGTTAAATGACGAACAGCTTCTTTTGGAAGCTAGTCAGTTATCTGATATGTATCATCAGCTGACTCT
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AAGTTACATGACGTTGGACTGCTTAATGCAGATAACATCAAGCTTATTGCAAAGTATTCTGGCATTGCGGAAGCTCAACTTCGCT
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CAGTACTATCCAAGACGACCTATCTAACTATGCTAGACAAGCTATTGATGATGTGCATAATTTGACTAACACCACCTTGCCATTTA
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CTATTACTCAAAAAAAGCTACAGCTAGAGAGATGTGTGCACCTTTGCAACATCAAATTGTCACTACTGGCGAAGCGAGAGAAGA
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TGCGAATGCGCAAGCTAAGCAGAGGGCAATCGAGAGATCAATACGTAAGAGTAAAGAGCTACTGCACGTTGCGAAGCAATTGG
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TTACATCGCAATCAAGCCAGAGAAAAGCGTTACAATAATCCTTATACCAAAACTCAAAGTGAAGTCGAAGTTAGAAAAGAAAAAG
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SPy0702
Seq ID 31
ATGAGCAGAGACCCAACACTTATTTTAGACGAGTCAAACCTCGTTATTGGTAAGGATGGACGTGTGCATTACACATTTACCACAG
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TAATTTTAATAGCAAAAACAATGCCTTAGTACGTAAAGATGGCACACATACTGCCTTTGTACATTTTAGTAATGCGACGCCCAAA
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CTGTGAATAGGGAATTGAATAACTACATCACAAAAATTTAA

SPy0710
Seq ID 32
ATGACCTTTTTAGATAAAATTAAACAAGGCTGTTTAGATGGCTGGGCTAAGTACAAAATCTTGCCATCCTTGACCGCAGCACAAG
CTATCTTAGAGAGCGGGTGGGGCAAACATGCCCCACACAACGCTCTGTTTGGTATTAAGGCAGATAGCTCTTGGACTGGTAAAT

CATTTGATACCAAAACCCAAGAGGAATATCAAGCAGGTGTTGTCACGGATATTGTGGACCGATTTAGGGCGTATGATAGTTGGG
ATGAGTCGATAGCTGATCACGGACAATTTTTAGTTGATAATCCACGCTATGAGGCAGTTATTGGGGAGACTGACTATAAAAAGG
CTTGTTACGCTATTAAAGCAGCTGGATACGCTACGGCAAGTAGCTATGTCGAACTTTTAATCCAACTGATTGAGGAAAACGACTT
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GAGCCGCAAACTTCTGACACTATCGTAGAGACAGCAAAAACAGGCACCTTTACCCTTGATGTTGCAGAGATCAATATCAGACGC
TGGCCAAGTCTAGCCAGCGAGGTTGTAGGTATCTACAAGCAAGGTGATACTGTCAGCTTTGATAGCGAGGGCTACGCTAATGG
CTATTATTGGATTAGCTATGTTGGAGGCTCAGGTATGCGTAACTACCTAGGTATTGGACAGACTGATAAAGATGGGAATCGCAT
CAGCCTTTGGGGTAAATTAAATTAG

SPy0711
Seq ID 33
ATGAAAAAGATTAACATCATCAAAATAGTTTTCATAATTACAGTCATACTGATTTCTACTATTTCACCTATCATCAAAAGTGACTCT
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TCAACGACACACACATTAAACATTGATACTCAAAAATATAGAGGGAAAGACTATTATATTAGTTCCGAAATGTCTTATGAGGCCTC
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AACAAAATTATTCTAGAAAAAGATATCGTAACTTTCCAGGAAATTGACTTTAAAATCAGAAAATACCTTATGGATAATTATAAAATT
TATGACGCTACTTCTCCTTATGTAAGCGGCAGAATCGAAATTGGCACAAAAGATGGGAAACATGAGCAAATAGACTTATTTGACT
CACCAAATGAAGGGACTAGATCAGATATTTTTGCAAAATATAAAGATAATAGAATTATCAATATGAAGAACTTTAGTCATTTCGAT
ATTTATCTTGAAAAATAA

SPy0720
Seq ID 34
ATGATAACAACTTTTGAAACAATTTTAGATAAAATAAAAGCTCACCAAACTATTATTATCCATCGCCATCAAAATCCTGACCCTGAT
GCTCTTGGTAGTCAGGCCGGCTTGAAAGAAATTATTGCACAAAATTTCCCAGACAAAAAGGTTTTGATGACTGGTTTTGATGAGC
CTAGTTTAGCTTGGATTAGCCAAATGGATCAGGTGACTGACAAAGACTATAAAGAGGCTTTGGTCATCATTACAGATACAGCGAA
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TGACTTCTATTATGTGGACACAAGCGCTTCTAGCGCAAGTGAAATCATTGCAGACTTTGCCTTTAGTCAGAATCTTACTCTCTCT
GACAAGGCTGCTAAGCTCTTATACACCGGTATCGTTGGTGATACAGGGCGATTTCTTTATGCCTCAACCACTAGTAAAACCCTTT
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GCTGCAAAGCTACGTCTTTGAGCATTTAACAATTGATGAGAGTGGGGCTGCTTATGTCCTTGTCAGCCAAGAAACCTTAAAACAT
TTTGACGTGACCCTAGCAGAAAGCTCTGCCATTGTCTGTGCTCCTGGTAAAATTGATAACGTTCAAGCTTGGGCTATTTTTGTTG
AGTTAACTGACGGCAACTACCGTGTGCGTATGCGCAGTAAAGAAAAGATTATTAATGGCATTGCTAAGCGTCACGGTGGAGGG
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GAGATTTAG

SPy0727
Seq ID 35
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TTGACGAAGCATTAGCAGGTTTTGCCTCTCATATTAAAGTCTTTATTGAAGCAGATAATTCCATTACAGTAGTAGATGATGGCCG
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CGTGTTTATAAAAACGGCCAAATTCATTACCAAGAATTTAAACGCGGGGCTGTTGTAGCAGATCTTGAGGTCATTGGAACCACT
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GACGCTAACCAAAACGAACTTTTCATCGTCGAAGGAGATTCAGCGGGTGGGTCGGCCAAATCAGGTCGTAACCGAGAGTTTCA
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GCCGATGTGGATGGCGCTCATATTAGAACCTTACTTTTAACCTTGATTTACCGCTTTATGAGACCTGTTCTAGAAGCTGGCTATG
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CCAATTAAAAACAGCTCTTGAAAAATATAGTATTGGTCGTTCAAAACCAACTGTTCAACGTTATAAAGGTCTTGGGGAAATGGAT
GACCATCAACTTTGGGAAACTACTATGGATCCTGAAAATCGTTTGATGGCGCGTGTGACAGTTGATGATGCCGCAGAAGCAGAT
AAAGTATTTGATATGTTAATGGGAGATCGTGTTGAACCAAGACGTGATTTCATTGAGGAAAATGCGGTTTATAGTACACTGGATA
TTTAG

SPy0737
Seq ID 36
ATGCGTAAGGTCAAAAAAGTCTTTGTTAGTTCATGTATGCTTTTAACAGTGGGCCTCGGAGTTGCCGTACCTACTGGATTCAGCC
AATCTAATGGCGTGATGGTTGTAAAGGCTGCGGAAGTGCCGGCGACAGATTTATCACGTCAGGCGTCTGATTCGGAGAGGGTA
GATGAATCGTCTTTATTGCAGAAAGAAAACTTATCAGTAGATTCATTTAAATTAGAAAATTTAAATGGATGGGAAGCTGAAAATGA
TACAGCAGGTAATTTGGGGAAATTTAAAGATCCAGATAGTTCGGGCTATCAAAATATTTTGACATCATCTGGAAAGAATATCAGT
GTAGCTGTTGCTCCCAAAGGTTCAGGTAAAATGAACATTAAAGTAACTAAAAGATCAAATTTTCAGGGTGGATATTATGTAGGTG
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AGTTCAAAACGAGAGTTAAGCCCGTTGAATCTAATAATAAACTAGGGAAAGAGCTTGTTATTAGGGTGGATAATAAAAATGTATC
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CGTTTGATGGCGATATCCTAAGAGTTTATAAAGATAGCAAAATCATTGCTAGAACAGTAATAAAAGGCAATAAGTGGGATGTTAA
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TTTCTGAGAATGAAGGTAAGGGAAATTCTATTCCCGATAAATACAAATCTGGCAATAAAGATGATTTGGTAAATAAGGCTGAAGT
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AAGAAAAAGAAGAGCAATCTAAAGCTGTTGACGCTGAACTTAAGAAAGCGATAGAAGCTGTTAACGCAGCTGACACAGCTGACA
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GCTCATGGTAAGGAACTTGATAGAGTCGCTCAAGAAACTAAAGGTGCGATTGAAAAAGACCCTACTTTGACGACTGAAGAAAAA
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AAAGCTTACGGTGAAGGTGTTACAGACATCAAGAACCAACACAAGTCAGGTGACCCTGTCGACGCTCGTCGTGGATTACACAA
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CCTTAACAAAAGCTGATAAAGCTAAACAAACAGAAGCTGTTGCTAAAGCTCTTAAAGCTGCTATCGCAGCGGTTGATAAAGCGA
CAACAGCTGAAGGCATTAACCAAGAACTTGGTAAAGGCATCACAGCTATCAACAAAGCTTACCGTCCAGGTGAAGGTGTTGAAG
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ACAGCTGCTCTTAACGAAGCGAAACAAGCTGCTATTGAAGCTCTTAAACAAGCTGCGGCAGAAACACTTGCTAAGATTACAACT
GATGCTAAATTGACTGAAGCTCAAAAAGCTGAACAATCAGAAAATGTATCATTAGCGCTTAAGACGGCTATTGCGACTGTTCGTT
CAGCACAATCTATTGCGTCTGTGAAAGAAGCAAAAGATAAAGGTATTACTGCTATCCGTGCAGCCTATGTGCCTAATAAGGCAG
TCGCAAAATCATCGTCAGCGAACCATCTTCCAAAATCAGGTGATGCAAACTCAATTGTTCTTGTTGGCTTAGGAGTTATGTCTCT
TCTTTTAGGTATGGTGCTTTATAGCAAGAAAAAAGAAAGTAAAGACTAA

SPy0747
Seq ID 37
ATGATTAACAAGAAATGTATAATACCTGTTTCATTGTTGACACTAGCTATTACGCTTACTAGTGTTGAAGAAGTTACTTCACGCCA
AAATTTGACTTATGCCAATGAAATCGTAACACAAAGGCCAAAGAGAGAATCTGTTATTAGTGATAAATCGAATTTTCCCGTCATAT
CACCTTACCTAGCAAGTGTGGATTTTGGTGAGAGAAAAACACCTTTGCCAACACCTGATAAAGGAGTAAAAGTAACTACTGAACA
GTCTATTGCTCAAGTAAGAAAGGGGCCTGAAGAAAGACCCTATACTGTTACTGGCAAGATTACGAGTGTGATCAATGGCTGGGG
AGGCTATGGCTTTTATATTCAAGATAGTGAAGGTATTGGACTTTATGTTTATCCTCAAAAAGATTTAGGATACAGTAAGGGAGATA
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AATCATAG

SPy0777
Seq ID 38
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SPy0789
Seq ID 39

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SPy0839
Seq ID 40
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TATTAA

SPy0843
Seq ID 41
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SPy0872
Seq ID 42
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SPy0895
Seq ID 43
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SPy0972
Seq ID 44
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SPy0981
Seq ID 45
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SPy1008
Seq ID 46
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TGTAGATGTGTCAATCAGCTAA

SPy1032
Seq ID 47
GTGAATACTTATTTTTGCACACACCATAAACAATTACTACTTTATTCAAACCTATTCCTTAGCTTTGCTATGATGGGCCAAGGAAC
TGCCATTTATGCCGATACACTGACTTCAAATTCAGAACCTAATAATACTTACTTTCAAACGCAAACGCTCACTACTACAGATAGCG
AAAAAAAGGTAGTACAGCCACAACAAAAAGACTACTATACTGAATTGTTAGACCAATGGAACAGTATTATCGCAGGCAACGATGC
TTATGATAAAACCAATCCTGACATGGTCACTTTTCATAATAAAGCTGAAAAGGATGCTCAAAACATTATTAAAAGCTATCAAGGGC
CTGACCACGAAAATAGAACTTACCTTTGGGAACATGCAAAGGATTATTCCGCTTCTGCTAATATCACGAAAACTTACCGCAATAT
TGAAAAAAATAGCAAAACAGATCACTAATCCTGAATCATGCTATTATCAAGATAGTAAAGCTATTGCTATTGTAAAAGACGGTATGG
CCTTCATGTATGAACACGCTTATAATCTAGATCGTGAAAATCATCAAACAACTGGAAAAGAAAACAAAGAAAATTGGTGGGTTTA
TGAAATTGGAACTCCTCGTGCTATTAATAATACCTTATCCTTGATGTATCCTTATTTTACTCAAGAAGAAATTCTTAAATACACAGC
TCCAATCGAAAAATTTGTGCCTGACCCTACTCGTTTTAGGGTTCGCGCTGCCAATTTTTCACCTTTTGAAGCCAATAGCGGAAAT
TTAATTGATATGGGGCGTGTTAAACTCATTTCCGGTATTCTTCGTAAAGATGATCTCGAAATTAGTGATACAATCAAAGCAATTGA
GAAAGTTTTCACGCTAGTTGATGAAGGAAATGGTTTTTACCAAGACGGTTCTTTAATTGATCACGTGGTTACTAACGCTCAAAGT
CCACTTTATAAAAAAGGCATTGCTTACACTGGAGCTTACGGTAATGTGCTTATAGATGGCTTATCGCAATTAATTCCTATTATTCA
AAAAACAAAGTCTCCTATAAAAGCGGATAAAATGGCTACTATCTATCATTGGATTAACCATTCTTTTTTCCCTATCATCGTTCGTG
GAGAAATGATGGATATGACTCGAGGGCGTTCTATCAGTCGTTTTAATGCCCAATCTCATGTTGCTGGCATTGAAGCACTTCGTG
CTATTTTACGTATTGCTGACATGTCTGAAGAGCCTCACCGTTTGGCACTTAAAACACGTATAAAAACACTCGTCACACAAGGGAA
TGCTTTTTACAATGTCTATGATAATTTGAAAACCTATCACGATATCAAACTTATGAAAGAACTACTAAGTGATACTTCTGTTCCAGT
CCAAAAACTTGATAGTTACGTAGCTAGTTTCAATAGTATGGATAAATTGGCACTATATAATAATAAACACGATTTTGCTTTTGGCC
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ACCTATACAATAACGATTTAGGACACTACAGTGAAAACTATTGGGCAACGGTAAATCCCTACCGCTTACCTGGAACCACAGAAA
CTGAGCAAAAACCACTAGAGGGAACTCCTGAGAATATTAAAACGAACTATCAACAAGTTGGCATGACTGGTCTCTCTGATGACG
CTTTTGTTGCAAGTAAAAAACTTAATAACACAAGTGCTCTAGCTGCTATGACCTTCACTAATTGGAATAAAGCCTCACCCTCAAT
AAAGGGTGGTTTATCTTAGGAAACAAAATAATCTTTGTTGGTAGCAATATCAAAAACCAATCATCTCACAAGGCGTATACAACTAT
TGAACAACGAAAAGAAAATCAAAAGTACCCTTACTGTTCTTATGTTAACAATCAACCCGTTGACTTGAATAATCAGCTAGTTGATT
TTACAAACACTAAAAGTATTTTCCTTGAAAGTGATGATCCCGCTCAAAATATTGGTTACTACTTCTTCAAGCCAACAACACTTAGC
ATAAGTAAGGCACTTCAAACAGGGAAATGGCAAAACATAAAAGCTGATGACAAATCACCAGAAGCCATCAAAGAAGTTTCAAATA
CCTTTATCACTATCATGCAAAACCATACTCAAGATGGCGATCGTTATGCCTATATGATGCTTCCAAATATGACTCGTCAAGAATTT
GAAACCTATATTAGCAAGCTTGATATCGACTTATTAGAAAACAATGACAAACTGGCCGCTGTCTACGATCATGATAGTCAACAGA
TGCACGTCATTCACTATGGAAAAAAAGCAACGATGTTTTCAAATCATAATCTTTCTCATCAAGGCTTTTATAGTTTTCCTCATCCT
GTCAGGCAAAATCAACAATAA

SPy1054
Seq ID 48
TTGCTGACCTTTGGAGGTGCAAGTGCGGTTAAGGCGGAAGAAAATGAAAAAGTAAGAGAGCAAGAAAAGCTCATACAGCAACTT
TCTGAAAAGCTAGTGGAAATTAATGACTTACAAACTTTAAATGGTGATAAAGAGAGTATACAGTCTCTCGTAGATTATCTGACTCG
AAGAGGAAAACTTGAAGAAGAATGGATGGAATATTTGAATTCTGGTATTCAACGCAAACTTTTTGTTGGTCCAAAAGGACCTGCA
GGTGAAAAAGGAGAACAAGGTCCTACTGGAAAACAAGGCGAGCGTGGTGAGACCGGCCCTGCAGGTCCACGTGGTGACAAGG
GCGAAACTGGTGACAAAGGAGCCCAGGGTCCAGTAGGTCCCGCTGGCAAGGACGGCCAAAACGGTAAAGATGGTCTTCCAGG
TAAAGACGGCAAGGACGGCCAAAACGGTAAAGATGGTCTTCCAGGTAAAGACGGCAAGGACGGCCAAGACGGTAAAGATGGC
CTCCCAGGTAAAGACGGTAAGGATGGCCAAAATGGCAAAGATGGTCTTCCAGGTAAAGACGGTCAACCAGGTAAACCAGCTCC
TAAAACACCAGAGGTCCCTCAAAACCCAGATACTGCACCACATACTCCAAAAACCCCTCGGATCCCTGGTCAATCAAAAGACGT
GACACCTGCTCCTCAAAACCCTTCTAATAGAGGTCTAAACAAACCACAAACACAAGGTGGTAATCAGCTCGCAAAAACACCGGC
AGCTCACGACACACACAGACAATTGCCAGCAACAGGCGAAACAACCAATCCATTCTTTACAGCAGCTGCTGTAGCTATCATGAC
GACAGCTGGAGTTGTAGCTGTTGCAAAACGTCAAGAAAACAACTAA

SPy1063
Seq ID 49
ATGTATATATTCTCATCGTCAAAAAAAGATAGTGCTAAAGAATTAGTTATCTTGACTCCTAATAGCCAAACTATTTTAACAGGGAC
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AAAAGATAAACCATTAAACGCTGATATTTTCTTTGGTGGCAATTACACTCAATTTGAAAGCCATAAAGATTTATTTGAATCTTATGT
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ATTGTTAATAACGAATTAGCAAGAGGACTTCATATTACCAGTTATGAGGATTTGCTACAACCAGCTTTAAAAGGCAAAATTGCTTT
TGCTGATCCCAACAGTTCATCAAGTGCCTTCTCACAGCTGACTAATATATTGTTAGCTAAGGGGGGGTACACAAACGCTGACGC
TTGGGCTTACATGAAGCGCTTGTTGGTCAATATGAATTCTATTAGGGCTACGAGTTCTTCAGAAGTCTATCAATCTGTCGCTGAG
GGTAAGATGATTGTTGGGCTAACCTACGAAGATCCTTGTATCAACCTGCAAAAAAGTGGTGCCAATGTTTCCATTGTTTATCCAA
AAGAAGGAACGGTGTTTGTGCCCTCCTCTGTTGCTATTATCAAACATGCGCCAAACATGACAGAGGCTAAGCTCTTTATTAATTT
TATGTTATCACGTGATGTGCAAAATGCCTTTGGCCAATCAACCAGTAACCGACCCATTCGTCAAGATGCCCAAACCAGTCACGA
CATGAAAGCCTTAGAAACGATAGCTACTTTGAAAGAGGATTATGCTTATGTTACCAAGCACAAGAAAAAAATAGTGGCTACGTAC
AACCAGTTGCGCCAACGGTTGGAAAAAGCTAAGTAG

SPy1162
Seq ID 50
ATGCCGACTAGTATTAAAGCTATTAAAGAAAGCTTAGAGGCCGTTACTAGCCTCTTGGACCCCCTCTTTCAAGAATTGGCAACC
GACACTAGGTCAGGCGTCCAAAAAGCTCTAAAAAGCCGACAAAAGGTTATTCAGGCCGAGTTAGCAGAAGAAGAACGATTAGA
AGCCATGCTTTCTTATGAAAAAGCTCTTTATAAAAAAGGTTATAAAGCCATTGCAGGTATTGATGAGGTGGGACGTGGTCCCTTA
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CTAAGCATGAGACCATTTATCAGGCAGTGAAAGAAAAGGCTTTGGCTATCGGTATCGGTATTATTGACAATCAGCTTATTGATGA
GGTCAATATTTATGAAGCAACCAAACTGGCCATGCTAGAAGCCATTAAACAGTTGGAGGGCCAACTCACACAACCAGATTATCT
CTTGATTGATGCCATGACATTGGATATTGCTATTTCGCAGCAGTCTATTCTTAAAGGCGATGCCAATTCCTTGTCTATTGCAGCA
GCATCAATTGTAGCTAAGGTCACCAGAGATCAGATGATGGCTAACTATGATCGCATTTTTCCTGGTTATGACTTTGCTAAAAATG
CAGGCTATGGCACCAAAGAACATTTACAGGGATTAAAAGCTTACGGCATAACGCCTATCCATCGTAAAAGTTTTGAACCTGTTAA
ATCCATGTGCTGCGATTCAACTAATCCTTAA

SPy1206
Seq ID 51
ATGACAGTTAAGGAAGAAACGATGAGTATTTTAGAAGTTAAGCAGTTGAGTCACGGTTTTGGGGATCGGGCTATTTTTGAAAATG
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AGGACATTTACAGCCTGACGAAGGAAAAGTAGAGTGGTCGAAGTATGTCACTGCAGGTTACCTGGATCAACATACAGTGTTGGA
ATCAGGACAAACCGTTCGTGATGTCTTGCGAACTGCTTTTGATGAGTTATTTAAGACCGAGAATCGTATTAATGAGATTTACGCG
TCAATGGCAGATGATAAAGCTGATATTGCTGTTTTGATGGAAGAAGTAGGTGAGCTTCAAGATCGTTTAGAAAGTCGTGATTTCT
ATACTTTGGATGCTAAGATTGATGAAGTAGCGCGTGCGCTTGGTGTTATGGATTTTGGAATGGAGTCAGATGTTACATCCTTATC
AGGTGGGCAACGAACAAAGGTTTTATTAGCCAAATTACTATTAGAAAAACCTGATATTCTGCTATTAGATGAACCAACTAACCATT
TGGATGCTGAGCATATTGAATGGTTAAAACGCTATTTACAACATTATGAAAATGCTTTTGTGTTGATTTCGCATGATATTTCTTTCT
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ATGAGATGAAACAATCTCAACTTGAAGCAGCCTATGAACGTCAACAAAAAGAGATTGCTAACTTGCAGGATTTTGTCAACCGAAA
TAAGGCTCGGGTAGCGACACGTAACATGGCAATGTCTCGCCAAAAAAAACTTGATAAGATGGATATAATTGAACTTCAAGCTGA
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ATCTACTTTGCTAAAAAGTTTATTAGGTGTTATTGAGCCTTTAGAAGGTCATATTGTCACAGGGGATTTTTTAGAAGTTGGCTACT
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TTCGAGCGGCACTAGCTCGTTGCGGACTAACATCAAAACATATCGAAAGTCAAATTCAAGTACTTTCGGGTGGTGAACAAGCAA
AAGTTCGTTTTTGTTTGTTGATGAATCGTGAAAATAACGTGCTTATTTTAGACGAACCAACAAATCATCTTGATATTGATGCTAAA
AATGAGCTCAAACGTGCTTTAAAAGCATATAAGGGTTCTATTTTAATGGTTTGTCATGAACCTGATTTCTACAATGGGTGGGTAA
CCGATACTTGGGATTTTAGTAAGTTAACCTAA

SPy1228
Seq ID 52
ATGAACAAGAAATTTATTGGTCTTGGTTTAGCGTCAGTGGCTGTGCTGAGTTTAGCTGCTTGTGGTAATCGTGGTGCTTCTAAAG
GTGGGGCATCAGGAAAAACTGATTTAAAAGTTGCAATGGTTACCGATACTGGTGGTGTAGATGACAAATCATTCAACCAATCAG
CATGGGAAGGCCTGCAATCTTGGGGTAAAGAAATGGGCCTTCAAAAAGGAACAGGTTTCGATTATTTTCAATCTACAAGTGAAT
CTGAGTATGCAACTAATCTCGATACAGCAGTTTCAGGAGGGTATCAACTGATTTATGGTATCGGCTTTGCATTGAAAGATGCTAT
TGCTAAAGCAGCTGGAGATAATGAAGGAGTTAAGTTTGTTATTATCGATGATATTATCGAAGGAAAAGATAATGTAGCCAGTGTT
ACCTTTGCCGACCATGAAGCTGCTTATCTTGCAGGAATTGCAGCTGCAAAAACAACAAAAACAAAAACAGTTGGTTTCGTGGGC
GGTATGGAAGGAACTGTCATAACTCGATTTGAAAAAGGTTTTGAAGCAGGAGTTAAGTCTGTTGACGATACAATCCAAGTTAAAG
TTGATTATGCTGGATCATTTGGTGACGCTGCAAAAGGAAAAACAATCGCAGCAGCTCAGTATGCAGCAGGTGCTGATGTTATTT
ACCAGGCAGCAGGAGGCACTGGAGCAGGTGTATTTAATGAAGCAAAAGCTATTAATGAAAAACGTAGTGAAGCTGATAAAGTTT
GGGTTATTGGTGTTGACCGTGATCAAAAAGACGAAGGAAAATACACTTCTAAAGATGGCAAAGAAGCAAACTTTGTACTTGCATC
ATCAATCAAAGAAGTCGGTAAAGCTGTTCAGTTAATCAACAAGCAAGTAGCAGATAAAAAATTCCCTGGAGGAAAAACAACTGTC
TATGGTCTAAAAGATGGCGGTGTTGAAATCGCAACTACAAATGTTTCAAAAGAAGCTGTTAAAGCTATTAAAGAAGCGAAAGCAA
AAATTAAATCTGGTGACATTAAAGTTCCTGAAAAATAG

SPy1245
Seq ID 53
ATGAAAATGAAAAAAAAATTCTTTTTGTTAAGTCTTTTGGCCCTATCAACTTTCTTTTTATCCGCATGTTCTAGCTGGATTGATAAA
GGTGAGTCAATAACCGCTGTAGGATCAACAGCACTACAACCCTTAGTAGAAGCAGTAGCTGATGAATTTGGAAGCAGTAATCTA
GGCAAGACTGTCAATGTTCAAGGTGGTGGTTCAGGTACAGGGTTGTCTCAAGTTCAATCAGGAGCTGTCCAAATTGGAAATAGT
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CCAATCCTAAAGTCAAGGTTTCCAATCTCAGTAGTCAGCAGTTGCAAAAGATTTTTTCAGGAGAATATACCAATTGGAAACAAGT
TGGAGGAGAAGATCTTGCGATTTCAGTGATCAACCGAGCAGCAAGTTCTGGCTCACGAGCAACCTTTGACAGTGTTATCATGAA
AGGGGTCAACGCTAAACAAAGTCAAGAGCAAGACTCCAATGGGATGGTTAAATCGATTGTTTCACAAACACCAGGTGCCATTTC
TTACCTTTCCTTTGCCTACGTTGATTCATCTGTTAAATCTTTGCAATTAAATGGGTTTAAGGCAAATGCTAAGAACGTGGCTACAA
ATGATTGGCCAATCTGGTCCTACGAACACATGTATACCAAAGATAAACCAACAGGGTTGACCAAGGAATTTCTTGATTATATGTT
TTCAGATGAAGTACAACAGAACATTGTTACACATATGGGATATATTTCGATAAATGATATGGAAGTGGTCAAATCTCATGATGGA
AAAGTAACAAAAAGGTAA

SPy1315
Seq ID 54
ATGACGCACAAAATAAAAGTATTGCTGCTTGCGATAATGTCTATTTTTTTGACATGCAATATTGCAAGTGCTGAAACTATTGCTAT
TGTTTCAGATACAGCTTATGCCCCATTTGAATTTAAAGACTCAGATCAAATTTACAAAGGAATTGACGTTGATATTATTAATGAAG
TAGCCAAACGTCAATCTTGGGATTTCAGTATGAGTTTCCCGGGTTTTGATGCAGCTGTAAATGCTGTTCAATCTGGTCAAGCGA
GTGCTCTAATGGCCGGTACAACCATTACGAATGCTCGTAAGAAAGTCTTTCATTTCTCAGAGCCATATTACGATACCAAAATTGT
CATTGCGACACGTAAAGCCAATGCCATCAAAAAATACAGTGACTTAAAAGGAAAAACGGTCGGTGTTAAAAATGGAACAGCGGC
TCAAGCCTTTTTGAATAACTATAAAAAAAAGTATGATTATACTGTTAAAACATTTGACACAGGTGATCTTATGTATAATAGTTTATC
TGCTGGTTCTATTGCCGCTGTTATGGATGATGAGGCGGTTATCCAATACGCAATCAGCCAAAACCAAGATATTGCTATTAACATG
AAAGGAGAGCCCATTGGAAGCTTTGGGTTTGCTGTCAAAAAGGGAAGCGGATATGATTATCTAGTTAATGATTTCAATACAGCTC
TTAAAGCTATGAAAGCTGATGGTACCTACCAAGCTATCATGACCAAGTGGTTAGGCACAGATGATAAAGCTACCACCAGTCAGG
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CTAATCCAGGTTTCGATGCTGCCTTAAATGCTGTGCAATCTAGCCAAGCAGATGGGGTCATTGCTGGTGCAACTATTACTGACG
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ATGAAGACTTAGACAGAAAAACAGTCGGTGCTAAAAACGGCACTTCATCTTACTCTTGGTTAAAAGAAAACGCTCCTAAATATGG
TTATAATGTCAAGGCATTTGATGATGGTTCTAGCATGTATGATAGCTTAAATTCAGGTTCTGTAGATGCTATCATGGATGATGAG
GCGGTTCTTAAATACGCTATCTCTCAAGGTCGTCGCTTTGAAACACCTCTTGAGGGCATTTCTACTGGTGAAGTTGGTTTTGCTG
TCAAGAAAGGAACTAATCCAGAATTAATCGAAATGTTCAACAATGGCTTAGCTGCTCTCAAAAAATCTGGTCAGTATGATGACAT
TATAGATAAATACCTTGACTCTAAGAAAGCTGCAACTCCTTCTGAAAAAGGTGCTGATGAGTCTACTATTTCAGGCCTATTATCAA
ATAACTACAAACAACTATTGGCAGGACTTGGAACCACGCTCAGTTTAACCCTTATTTCATTTGCTATTGCTATAATTATCGGGATC
ATCTTTGGGATGATGGCCGTGTCACCAACTAAATCACTTCGACTTATTTCAACGGTCTTTGTGGACGTTGTTCGAGGGATTCCTT
TGATGATTGTGGCTGCCTTCATTTTCTGGGGAGTACCAAACCTTATCGAGAGTATGACCGGCCACCAGTCACCGATTAATGATT
TCTTAGCTGCTACAATTGCACTGTCACTTAATGGCGGAGCCTATATTGCTGAAATTGTTCGCGGTGGTATCGAAGCTGTTCCAG

CAGGGCAAATGGAAGCTAGTCGAAGTCTTGGTTTGTCTTACGGAACCACGATGAGAAAAGTAATTCTCCCACAAGCTGTGAAAC
TAATGTTACCTAACTTTATCAATCAGTTTGTTATTTCATTGAAGGATACAACAATCGTCTCAGCAATTGGTTTAGTGGAACTCTTC
CAAACAGGTAAAATCATTATTGCTAGAAATTACCAGTCGTTCCGTATGTATGCTATTTTAGCAATTATTTACCTTATCATGATTATA
CTCTTAACAAGACTTGCAAAACGTTTAGAAAAGAGGCTTAACTAA

SPy1357
Seq ID 55
ATGGGAAAAGAAATAAAAGTGAAATGCTTTTTGCGTAGATCAGCTTTTGGATTAGTTGCGGTGTCAGCATCAGTATTAGTCGGTT
CAACAGTATCTGCTGTTGACTCACCTATCGAACAGCCTCGAATTATTCCAAATGGCGGAACCTTAACTAATCTTCTTGGCAATGC
TCCAGAAAAACTGGCATTACGTAATGAAGAAAGAGCCATTGATGAATTAAAAAAACAAGCTATTGAGGATAAAGAAGCTACGACA
GCTATAGAAGCAGCAAGTTCAGATGCCTTAGAAGCATTAGCGGATCAAACAGACGCTTTACAATCAGAAGAAGCTGCGGTTGTT
AAAGCGGATAACGCTGCTAGTGACGCCTTAGAAGCATTGGCGGATCAAACAGACGCTTTACAATCAGAAGAAGCTGAAGTAGTT
CAATCAGATAACGCTGCTAGTGACGCCTGGGAAAAAGCAGCAACTCCAATCGCTTTAGATGTTAAGAAAACTAAAGATACAAAA
CCTGTAGTTAAAAAAGAAGAAAGACAAAACGTTAATACCCTTCCTACAACTGGTGAAGAGTCTAACCCATTCTTTACAGCTGCTG
CGCTTGCAATAATGGTAAGTACAGGTGTGTTAGTTGTAAGTTCAAAGTGCAAAGAAAATTAG

SPy1361
Seq ID 56
ATGAAAACGAAAAAAAGTTATTATTTTAGTTGGTCTATTGTTATCATCTCAGTTGACTTTGATAGCTTGTCAATCACGAGGTAATGG
TACATATCCCATTAAAACGAAACAATCACGTAAGGGAATGACGTCAAACAAAATTAAACCGATTAAAAAAAGCAAAAAGACAAAC
AAGACTCACAAAGGTGTGGCGGGTGTCGATTTTCCTACAGATGATGGGTTTATTTTAACCAAAGACTCAAAAATCTTATCAAAAA
CAGATCAGGGAATCGTTGTTGACCATGATGGTCATTCGCATTTTATTTTTTATGCCGATTTAAAGGGAAGTCCATTTGAATACCTT
ATTCCAAAAGGAGCAAGTTTAGCTAAGCCAGCTGTTGCTCAGCGAGCAGCTAGTCAAGGGACTTCTAAAGTAGCAGATCCTCAT
CACCATTATGAATTTAACCCAGCGGATATTGTGGCTGAAGATGCTTTAGGCTACACGGTTCGCCACGATGATCACTTCCATTATA
TTTTGAAGTCAAGCTTATCAGGTCAGACACAGGCACAAGCTAAACAGGTTGCTACTCGCTTGCCACAAACCAGTAGCCTTGTTT
CAACAGCTACAGCTAATGGTATTCCAGGCTTGCATTTCCCAACCTCAGATGGTTTTCAATTTAACGGTCAAGGTATTGTTGGGGT
AACAAAAGACAGTATTTTAGTGGACCACGATGGTCACTTACATCCTATTTCTTTTGCGGACCTTCGTCAGGGTGGCTGGGCACA
TGTGGCAGATCAATACGATCCCGCTAAAAAAGCAGAAAAGCCAGCAGAAACCCATCAGACACCAGAGCTATCTGAACGTGAAAA
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CACATGCTATTGAGCATGCCCGTGAATTGGAAAAACATAAGGTTGGAATGGATACCTTGCGTGCCTTAGGGTTTGATGAAGAAG
TGATTTTGGATATCGTTCGCACTCACGATGCTCCAACCCCATTCCCATCAAATGAAAAAGATCCGAATATGATGAAAGAATGGTT
AGCAACGGTTATCAAACTTGACTTGGGCAGCCGTAAAGATCCTTTGCAACGTAAAGGACTTTCACTGTTACCCAACTTAGAAACT
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GGTGACTGATTATAGATTTTTGGATAATATGCCACAGTTAGAAGGCATTGATATTTCACAAAACAATCTCAAAGATATTAGTTTCT
TGAGCAAATATAAAAACTTAACTCTAGTAGCGGCTGCTGATAATGGTATTGAAGATATTAGGCCGCTTGGTCAATTACCAAATCT
CAAATTCCTCGTATTGAGTAACAATAAGATTTCTGATTTAAGCCCACTGGCATCGTTACATCAATTGCAAGAATTGCACATTGATA
ATAATCAGATTACAGATTTAAGCCCTGTTTCTCATAAAGAATCATTGACGGTTGTTGATTTATCAAGAAATGCTGATGTTGACTTA
GCAACACTTCAAGCACCCAAATTAGAAACGTTAATGGTCAATGATACCAAGGTTTCTCATTTGGATTTCTTGAAAAAATAATCCTAA
TCTATCTAGCCTATCTATTAACCGTGCGCAATTGCAATCTCTTGAAGGTATTGAAGCAAGTAGCGTCATTGTCAGAGTAGAAGCA
GAAGGTAACCAAATTAAATCGCTTGTGCTTAAAGACAAGCAAGGGTCACTTACTTTCTTGGATGTGACAGGCAACCAGTTGACTT
CTCTAGAAGGTGTTAATAATTTTACAGCACTTGACATTTTAAGCGTGTCTAAAAACCAATTAACAAATGTCAACCTATCTAAACCC
AATAAGACAGTTACTAACATTGATATTAGTCATAACAATATCTCATTAGCAGACCTTAAATTGAACGAGCAACATATTCCAGAAGC
CATTGCGAAAAACTTCCCAGCGGTTTACGAAGGTTCTATGGTAGGTAATGGAACAGCTGAAGAAAAAGCAGCTATGGCTACTAA
GGCGAAAGAAAGTGCTCAAGAAGCATCGGAATCACATGACTACAACCATAATCATACCTATGAAGATGAAGAAGGTCATGCTCA
CGAGCACAGAGACAAAGATGATCACGACCATGAACATGAGGATGAAAATGAAGCTAAAGATGAGCAAAACCATGCTGACTAA

SPy1371
Seq ID 57
TTGGCAAAACAATATAAAAATTTAGTGAACGGTGAATGGAAACTATCAGAAAACGAGATTACCATTTACGCACCAGCAACAGGTG
AAGAGTTAGGATCAGTTCCAGCGATGACGCAGGCAGAGGTAGATGCTGTTTACGCTTCAGCTAAAAAGGCTCTATCAGATTGGC
GCGCTTTGTCTTATGTGGAACGTGCAGCTTACCTTCATAAAGCGGCTGATATTTTAGTACGTGATGCTGAAAAGATCGGCGCGA
TTCTTTCAAAAGAAGTAGCCAAAGGTCACAAGGCAGCTGTCAGTGAAGTTATTCGTACCGCTGAAATCATTAATTATGCAGCAGA
AGAAGGGCTTCGTATGGAAGGTGAAGTTCTTGAAGGTGGTAGCTTCGAAGCTGCAAGTAAGAAGAAGATTGCTATTGTTCGTCG
TGAACCAGTTGGTTTAGTTCTTGCCATCTCACCTTTTAATTATCCCGTTAACTTGGCAGGTTCTAAAATTGCTCCAGCTCTTATTG
CAGGAAATGTTGTTGCTCTTAAACCACCAACACAAGGCTCTATTTCTGGTTTGTTACTAGCAGAAGCTTTTGCAGAAGCTGGTAT
TCCAGCAGGTGTCTTTAATACCATTACAGGGCGAGGTTCTGTTATCGGTGATTATATCGTTGAGCACGAAGCGGTTAGCTTTATC
AACTTTACAGGTTCTACTCCAATTGGGGAAGGAATCGGTAAATTAGCGGGTATGCGACCAATTATGCTTGAGCTTGGCGGTAAG
GATTCTGCTATCGTTTTGGAAGATGCAGATCTTGCTTTAGCAGCGAAAAATATTGTAGCCGGTGCTTTTGGTTACTCAGGCCAAC
GTTGTACAGCGGTTAAACGTGTTCTTGTGATGGACAAGGTGGCGGATCAATTGGCGGCTGAGATTAAAACACTTGTTGAAAAAC
TAAGTGTCGGAATGCCTGAAGACGATGCTGATATTACACCATTAATTGATACATCAGCTGCTGATTTTGTTGAAGGGTTGATTAA
AGATGCAACTGATAAGGGAGCTACTGCTTTGACAGCCTTTAATCGTGAAGGCAATCTTATTTCACCCGTTCTCTTTGATCATGTG
ACAACTGACATGCGTTTGGCATGGGAAGAGCCGTTCGGCCCAGTATTACCAATTATTCGTGTAACCACTGTAGAAGAAGCCATC
AAGATTTCTAATGAGTCTGAATATGGTTTGCAAGCTTCTATTTTTACAACTAATTTCCCAAAAGCTTTTGGCATTGCTGAGCAATT
AGAAGTTGGAACTGTTCACCTTAACAATAAAACACAACGTGGAACAGATAATTTCCCATTCTTAGGCGCTAAAAAATCAGGTGCA
GGGGTACAAGGAGTTAAATATTCTATCGAAGCTATGACAACTGTTAAATCTGTTGTATTTGATATCCAGTAA

SPy1375
Seq ID 58
ATGAGTCTCAAAGATCTTGGCGATATTTCATATTTTCGCCTAAATAATGAAATTAACCGTCCTGTTAATGGTAAAATTCCACTTCA
TAAAGACAAAGAAGCTTTAAAAGCTTTTTCCGCTGAAAATGTGCTGCCAAACACCATGTCTTTTACTTCCATTACGGAAAAAATTG
AGTATTTAATCTCAAATGATTACATTGAATCAGCTTTTATTCAGAAATACCGCCCTGAATTTATTACTGAATTAGATAGCATAATCA
AATCAGAAAATTTTCGCTTTAAATCATTTATGGCAGCCTACAAGTTCTACCAGCAATACGCCTTAAAAACAAATGATGGAGAGCAT
TATTTAGAAAACCTTGAAGACCGTGTCTTGTTTAATGCTTTGTATTTTGCAGATGGTCAAGAAGACTTAGCAAAAGATTTAGCCGT
TGAAATGATTAACCAACGTTACCAACCGGCTACTCCTTCCTTTTTAAATGCTGGTCGAAGCCGTCGTGGTGAATTGGTCTCTTGT
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TTGGGATTACCTTGTCTAACCTCCGTGAAGCTGGCGCACCAATCAAAGGCTATGCTGGTGCAGCCTCAGGAGTTGTTCCTGTTA
TGAAATTATTTGAAGATAGTTTTTCTTATTCAAATCAACTTGGGCAACGTCAAGGAGCTGGTGTTGTTTACCTAAATGTTTTTCAT
CCTGATATCATTGCTTTCTTATCTACTAAAAAAGAAAATGCCGATGAAAAGGTGCGTGTTAAAACCTTGTCACTAGGGATTACCG
TTCCTGATAAATTCTACGAATTAGCTCGTAAAAACGAGGACATGTATCTCTTTAGTCCTTACAATGTTGAAAAAGAATATGGCATT
CCCTTTAACTATCTCGACATTACCAATATGTACGATGAGTTAGTGGCGAACCCTAAAATTACTAAGACTAAAATTAAAGCTCGTGA
TCTTGAAACAGAGATTTCAAAATTACAACAAGAATCTGGTTACCCTTATATCATCAATATTGATACAGCTAATAAAGCTAATCCTAT
CGATGGAAAAATCATCATGAGCAACTTGTGTTCTGAAATTTTACAAGTTCAAACACCTAGCCTTATCAATGATGCGCAAGAGTTT
GTAGAAATGGGAACTGATATTTCATGTAACTTAGGTTCCACTAATATCCTGAACATGATGACCTCACCAGACTTTGGCCGTTCTA
TTAAGACCATGACACGTGCCCTAACTTTTGTTACTGATTCATCAAGCATTGAAGCTGTTCCAACCATTAAACATGGCAATAGCCA
AGCTCATACTTTTGGCCTTGGAGCTATGGGACTACATTCTTACCTTGCTCAACATCATATTGAATATGGCAGTCCAGAATCCATC
GAGTTTACTGATATTTACTTTATGCTCCTGAATTATTGGACCTTGGTCGAATCCAATAACATCGCTCGTGAGCGCCAAACTACCT
TTGTTGGCTTTGAGAACTCTAAGTACGCTAATGGTAGTTACTTTGATAAATACGTTACAGGACACTTTGTTCCAAAATCTGATTTG
GTGAAAGATCTGTTCAAAGACCATTTTATTCCGCAAGCTTCAGATTGGGAGGCTCTTCGCGACGCCGTTCAAAAAGATGGTCTT
TATCATCAAAACCGACTAGCAGTTGCTCCAAATGGCTCTATTTCTTATATCAATGACTGCTCTGCTTCTATTCACCCAATCACACA
ACGCATCGAAGAGCGTCAAGAAAAGAAAATTGGTAAAATCTACTATCCTGCAAATGGTTTGTCTACGGATACCATTCCTTACTAT
ACATCTGCTTACGATATGGACATGCGCAAAGTTATTGATGTCTATGCCGCTGCGACCGAACATGTGGACCAAGGCTTGTCATTA
ACTCTATTCCTTCGTAGTGAGTTGCCTATGGAGCTTTATGAGTGGAAAACACAAAGCAAACAAACCACTCGTGATTTATCCATCT
TACGAAACTACGCTTTCAATAAAGGCATTAAATCTATCTACTATATCCGTACCTTTACGGATGATGGGGAAGAAGTGGGCGCAAA
CCAATGTGAATCTTGTGTCATTTAA

SPy1389
Seq ID 59
ATGAAAGAATTATCGTCTGCACAAATCCGCCAAATGTGGTTGGATTTCTGGAAATCTAAAGGACATTGCGTTGAGCCTTCAGCTA
ACTTGGTTCCTGTGAACGACCCAACGCTTCTTTGGATCAACTCAGGTGTTGCAACCTTGAAAAAATATTTTGATGGTTCAGTGAT
TCCAGAAAATCCACGTATTACCAATGCACAAAAATCAATTCGTACTAATGATATTGAAAATGTTGGTAAAACAGCACGTCACCATA
CTATGTTTGAAATGCTTGGTAACTTCTCAATTGGAGACTATTTCCGTGATGAAGCTATTGAGTGGGGATTTGAACTCTTGACAAG
TCCAGACTGGTTTGATTTCCCTAAAGACAAGCTCTACATGACTTATTACCCAGATGACAAGGATTCGTATAACCGTTGGATTGCT
TGTGGCGTTGAACCAAGTCACTTGGTGCCGATCGAGGATAACTTCTGGGAAATCGGTGCTGGTCCTTCAGGTCCAGATACGGA
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ACATTGATACAGGTGCTGGTCTTGAACGTCTTGCAGCTGTTATGCAAGGGGCAAAAACAAACTTTGAAACTGACCTCTTCATGC
CAATCATCCGTGAAGTAGAGAAGTTGTCAGGTAAAACTTACGATCCAGATGGCGACAACATGAGTTTCAAGGTTATCGCTGACC
ACATCCGTGCGCTTTCATTTGCTATCGGTGATGGTGCGCTTCCTGGAAATGAAGGTCGTGGTTACGTTCTTCGTCGTCTTCTCC
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CAAACTTTATGATACTTATGGATTCCCGGTTGAATTGACAGAGGAATTGGCAGAAGATGCAGGCTACAAGATTGACCACGAAGG
CTTTAAGTCAGCCATGAAAGAACAACAAGACCGTGCGCGTGCAGCTGTTGTTAAGGGTGGTTCAATGGGGATGCAAAATGAAA
CCCTAGCTGGTATTGTTGAAGAATCACGATTCGAATACGACACATATAGTCTTGAATCAAGTCTTTCAGTCATCATCGCTGATAA
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TTGGTGAGAAATATGGTAAAGTGGTTCGTGTGGTTCAAATTGGTAATTATTCTGTTGAACTTTGTGGTGGAACTCACTTAAATAAT
TCTTCAGAAATCGGTCTCTTCAAGATTGTCAAAGAAGAAGGTATTGGTTCAGGCACTCGTCGTATTATTGCAGTTACTGGTAGAC
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CACTTCGTACATTTGCTGATAACTGGAAACAAAAAGACTACTCTGATGTGCTTGTTCTCGTAGCAGCTATTGGTGAGAAGGTTAA
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AA

SPy1390
Seq ID 60
ATGAAAAACTCAAATAAACTCATTGCTAGTGTTGTGACATTGGCCTCAGTGATGGCTTTAGCAGCTTGTCAATCAACTAATGACA
ATACTAAGGTTATTTCGATGAAAGGTGATACAATTAGCGTTAGTGATTTTTACAATGAAACAAAAAACACAGAAGTATCGCAAAAA
GCGATGCTAAATCTGGTAATTAGTCGTGTTTTTGAAGCTCAATATGGTGATAAGGTTTCAAAAAAAGAAGTTGAAAAGGCGTATC
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CCGCTCTTCAAAATTAGTAGAATATGCGGTTAAAGAAGCAGCTAAAAAAGAATTGACAACACAAGAATATAAGAAAGCATATGAA
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AAATGTACCGACTGATGTCGTAAAAGCGGCTTCAAGTTTGAATGAGGGTGGCATATCAGACGTTATCTCGGTTTTAGATCCAACT
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TTAAAGACAAAGCTTTTGCTAATATTTTGGCGCAATATGCAAATCTTGGTCAAAAAACTAAAGCTGCAAGTGAAAGTTCAACAACC
AGCGAATCATCAAAAGCTGCAGAAGAGAACCCATCAGAATCAGAGCAAACACAGACATCATCAGCTGAAGAACCAACTGAGACT
GAGGCTCAGACGCAAGAGCCAGCTGCACAATAA

SPy1422
Seq ID 61
GTGCTTTATCCAACACCCATTGCAAAGTTAATTGACAGTTACTCTAAACTTCCAGGAATTGGTATCAAGACGGCGACGAGATTAG
CCTTTTATACTATTGGAATGTCAAATGAAGATGTCAATGATTTTGCTAAAAACTTATTAGCAGCTAAAAGAGAACTGACCTATTGT
TCGATTTGTGGAAACCTTACCGATGACGATCCTTGTCACATTTGCACAGACACGAGTCGTGATCAGACGACCATTCTGGTAGTA

GAAGATGCTAAAGATGTTTCTGCCATGGAAAAAATCCAAGAGTATCATGGCTATTATCATGTGCTTCACGGCTTGATTTCGCCTA
TGAATGGTGTGGGGCCAGATGACATCAACCTTAAAAGTTTAATTACCCGTCTAATGGATGGTAAGGTGAGCGAAGTTATCGTAG
CTACCAATGCCACAGCAGATGGGGAAGCAACGTCCATGTATATTTCACGTGTCTTGAAACCAGCCGGGATTAAGGTAACTCGTT
TGGCAAGAGGTCTCGCAGTAGGTTCAGATATTGAGTATGCTGATGAAGTAACATTATTGAGAGCTATTGAGAATCGTACTGAACT
TTAA

SPy1436
Seq ID 62
ATGGATATGTCTAAATCAAATCGTCGTACTTGGCAAGGTTTAGTTGTTATTTTAATAGCTATTCTCACCACTTTTACCACAAGTAC
TGTTACGGCAGCCAGAAAAATTAGAAATTTCCCTGATACCACGGAAATTTTGTTAGGAACGAAGGCGACTGAGACACCAGGAAT
CTTACCATTCACTGGTAGCTACCAATTAGTTTTGGGCGATCTTGACAATCTGCAAAGGCCAACCTTCGCACACATCCAGCTAAAA
GATCAAGATGAGCCTAATATTAAACGAAAAGGACTTAAATTCAATCCTCCTGGCTGGCATAATTACAAATTGACTGACGCTAATG
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AATGACAAAATATCTTAATACTGGCTTTAGTGACAAAAATCCTTTAGGAATGCTCTATTATGAAAATAGATTAGATAGCTGGTTAG
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TATGTTGGAATTGATGAAAATGGAGATCTACTTCAAATTAAGTTAGGTAGTGAAAAAGAAAGTGTAGACAACTTTGGAGTAACAT
CAGTTACATTAGATAACGTATCTCCTTTAGCTGAATTGGATTACCAAACAGGAATGATGCTAGATTCAACTCAAAACGAAGAAGA
TAGTAATTTAGAAACCGAAGAGTTTGAAGAAGCGGCTTAA

SPy1494
Seq ID 63
ATGACTAGTAAAAAAGCGTGTTTATCAAGCATCATTGTGTTAGCAAGTTTAACGTGTGGAAATGATACTGTTAGTGCCAATCATCT
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TGGTCCTCGTCTCAAACAACTGATGATGCTGACAGAGACTATGAAGATTTTCTCGATGATGATTCTTTTATTTCTCAAAATGAAAC
TGATAAGATGTTTGAGAATTTAACTGATGATAGGTTATTAAATGAATTAGATGAATTAGATGAAGAAAATGAAGAAGATGAAGAAG
ATACAATTGAGCCAGAGCAAAATGTAATAATGCCTAGTGACGATGAGCTATTTGATTTAACTGATGCTGTTGAGACACGCCTTAC
TGTTTCTAGTGCTCCCCATTTAGAGGCTGAATTGCCGAAACCACATTTGAGGAGCCTATCAGATACAGCACTGCGGTCTGGTGA
AATTAGAGGACATTTAGATAACAAACTGGACGCTTTGTCTGTAACAGCTACAAAGTTAGCATTAACGATGGCTCAAAAATTTGATT
TGACAACGCATGTCTATTCTATAGGTGAAAGCTTTAGTGAAGTATTAGCTGCTCATTATGAAGACAGAAAAGCAGAATCAGCTTT
TTCTAAGAAAAAGAGATTTCACCTTCCTATTGCTACTCCAGATGTTGTTATAGAGGAGTTAAGGCGCCTAGTCTCTTCTATTGGA
AGTTCAAAAGAAGATGTTTCAGTTCCTTATAGTCGGAAGCTAGGTATGGCAGTTGCAAAAAGAAAAATAGCCCTGCCACAAACG
GGAGAGAGGTTCTCTTATTATCCAGTTTTACTTGGTTTAATGATATTAGGATTAACGCCGATTATGATACCAAAGAAGATAAATAA
TTAG

SPy1523
Seq ID 64
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CTGAAGCGGTTGAGCTTAAAACTGATGAGAAAACTGATAGTCAGGAAATTGAGTCAGAAACGACGTCAAAACCTAAAAAAACCA
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CGAAATCTTTCTTGATTCTTAATTTAAAAGATGAGAAAGCGATCCAACAGTTAGTTAAGCAATTAACGACATTACCTAAAAAATTA
GTCAAGAATATCAAGTCAGTGTCTCTTGCAAATTCCAAAACGACAGCGGATTTACTACTTATTGAAATGCATGACGGTAATGTAG
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AAGAAGGAGATAAGCCTGGTGAACATCAGGAACAGACAGACAATGATTCAGAAACGCCAGCAAATCAGAGTAGTCCTCAGCAA
ACACCACCATCCCCAGAAACGGTCCTCGAACAGGCCCATGGCTAG

SPy1536
Seq ID 65
ATGAAAAGACTTAAAAAAATCAAATGGTGGTTAGTGGGTCTGCTAGCTTTAATCTCTTTGTTGCTAGCGTTATTTTTTCCGCTACC
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TTACCAGTTTGTTGCAGTGGGCATTAGTCGTGCCAGCCTCGCTCAGCTATTATATGCTTGGCTGACACCGTTTACTGAAATTAGT
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CTATTTATCAAGCTTTATCCTTAGCTGGAAAACCAGTTACATTAGATTATAAAGGCGTATATGTTTTAGACGTAAACAACGAATCT
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GCAGCTGAAGCTGGTGCAGATATATTTTTTGTTCCGAATAATCCTGTTGATAAGGAAATTAAAAAAGTTAATCCAAATGCTATAAG
TAATTACGAAGAAGCCAAACGGGCAGCCAAACGACTAAAGACCAAAATGAAGATTGTTCCTGTTACGACTGTTCAAGAGGCACT
GGTTTATCTTCGCAAATAA

SPy1564
Seq ID 66
ATGTTGGAACACAAAATTGATTTTATGGTAACTCTTGAAGTGAAAGAAGCAAATGCAAATGGTGATCCCTTAAATGGAAACATGC
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TATGTACTTAAAGGTTCTATCAATGCTTATTTTGCTGAAAAGACTGGTTTTTCTCAGGAAGATGCTGAGGCTATTAAAGAAGTTTT

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GCTTATCAGATTCATCTAAATCAAGAAAAATTGGCTAAATATGAAGCGAAAGGGTTAACGCTTGAAATCCTAGAAGGACTCTAG

SPy1604
Seq ID 67
ATGGCAACTAAAAAAGTACATATTATTTCACACAGTCACTGGGATCGCGAGTGGTACATGGCTTACGAACAACACCACATGCGT
CTGATTAACTTAATAGATGACCTGTTAGAAGTTTTTCAAACGGATCCTGATTTTCATAGTTTTCATTTGGATGGGCAAACCATTAT
CCTAGATGATTATTTAAAAGTACGCCCCGAACGAGAACCTGAGATTAGACAAGCCATTGCTTCGGGAAAACTCCGTATCGGACC
TTTCTATATCTTACAGGACGATTTTTTGACCAGCAGTGAATCCAATGTGCGCAATATGCTGATTGGTAAGGAAGATTGTGACAGA
TGGGGCGCTAGTGTGCCACTTGGTTATTTTCCTGATACCTTTGGAAATATGGGACAAACACCACAGCTGATGTTAAAAGCCGGC
CTACAAGCTGCTGCCTTTGGTCGTGGCATTCGTCCAACTGGATTTAACAATCAGGTGGATACCAGTGAAAAATACAGCTCCCAA
TTCTCTGAAATCAGTTGGCAAGGCCCAGATAACAGTCGTATTCTTGGACTCCTCTTCGCCAACTGGTACAGCAATGGCAATGAG
ATCCCGACAACAGAAGCTGAGGCGCGTCTTTTTTGGGATAAAAAACTTGCTGATGCCGAACGCTTCGCCTCAACCAAGCACCTT
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TACGAATTTGTGCATTCCTGCTTTGAAGATTACTTGGCTGATCTCGCAGATGATTTACCAGAGAACCTTCAACCGTCCAAGGAG
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TGCGTTACGCTTGGAAAACCCTCATGCAAAATCACCCTCATGATTCTATCTGTGGTTGTAGTGTTGATAGCGTTCATCGGGAAAT
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GACCTGGAAAAAATATCATTTTGGCCAACGCTTTCCTAAAGAGGTTTACCAAGAAGCTCAAGAATATTTGGCAAGACTCTCCCAA
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CCTTAGCATTAAAGCTAGGAAATGAAACAACTCCTTCAGAAACCGTTTCCCTCTACGATGACAGTAATCAGTGCCTTGAAAATGG
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TCAAGCTTAACATCATTAGCAACACCGCTCAAGTTGCTGAACTTGAAATCCAGCAAACCTTTGCCATTCCTATCTCCGCAGATAA
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TAACAACCCTTATCCGCATGGAGAAAAATAATCCTCGCCTCCAATTCACCACACGTTTTGATAACCAAATGACTAATCATCGCTT
GCGCGTCCTATTCCCAACGCACCTTAAAACAGACCATCATCTAGCTGACAGTATTTTTGAAACTGTCAAACGTCCAAATCATCCA
GATGCCACCTTTTGGAAGAATCCAAGTAACCCACAGCACCAAGAATGCTTTGTGAGTCTCTTTGATGGTGAAAATGGAGTCACT
ATTGGTAACTATGGCCTCAACGAATATGAGATCTTACCAGATACCAACACCATTGCCATCACTCTCTTACGTTCTGTTGGCGAAA
TGGGCGACTGGGGTTACTTCCCAACACCTGAAGCCCAGTGTCTTGGCAAACACAGCCTTTCTTATAGTTTTGAAAGCATCACTA
AGCAAACACAATTTGCCAGCTACTGGCGAGCTCAAGAAGGCCAAGTCCCTGTTATTACCACACAAACAAACCAACACGAGGGAA
CATTAGCCGCAGAATATAGCTATTTGACGGGTACAAACGACCAAGTTGCCCTCACAGCTTTCAAACGTCGCTTAGCAGACAATG
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TAATTTGTTAGAAAAAGACAGCAAGCAAAGCACACCCAGCCAACTTGGCAAAGCGGAAATTTTAACTCTAGCTTGGAAGAAACA
ATAA

SPy1607
Seq ID 68
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GGCAAAAAATTTAGCCCTTTATTTTCTTTCCTTTCAACAACGCAGCAACAAGCAAGTTGCTGATTACCTGCGCAAGCATGAGATTG
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CCAAAATCAGTTAAATGGTGATAAAGGTCCCCAAGTCTTAAAACAAAAATTATTACAAAAAGGCATTGCAAGTCATGACATTGATC
CTATCTTATCTCAAACTGACTTTAGCCAACTCGCTCAAAAAGTAAGCCAAAAACTCTTTGACAAATATCAAGAAAAATTGCCACCA
AAAGCCTTGAAAGATAAAATCACCCAAGCATTACTGACCAAAGGCTTTTCATACGATCTAGCTAAACATAGCCTCAATCACCTTA
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GGTTATACCTTAAAGCAAAAGCTCTATCAGGCTCTCTACCGAAAAGGCTACAACAGCGACGACATTAATTGCAAGTTAAGAAATT
ATTTATAG

SPy1615
Seq ID 69
ATGATCTGTCTACTATGTCAACAAATTAGTCAAACACCAATAAGTATTACAGAAATCATCTTTTTAAGACGTATCTCTTCACCGATT
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AGTCAATATAAGTTTCAAGGAGACTATTTATTAAGAAAAGTTTTTGCAGTAGAACTTGCCGATGTTATCACCAAGTACTATAAAGG
CTATATCCCAGTCCCGGTTCCTGTAAGTCCCGGTTGTTTTCGAGAAAGACAATTTAATCAAGTGAGCGCTATTCTTGAGGCAGCT
AATGTTAGCTACCTTTCTCTTTTTGAAAAGCTAGATAATACTCACCAATCTTCCAGAACAAAAAAAGAGAGATTATTAGTAGAAAA
ATCTTATCGACTACTAAAAGTATCAAACATTCCTGATAAAATCCTTATAGTAGATGATATTTATACTACTGGTAGTACAATTATCGC
TCTTAGAAAACAATTGGCTAAAGTAGCAAATAGTGACATTAAAAGTTTGTCAATTGCACGTTAA

SPy1666
Seq ID 70
ATGAAATCCTTTTCTCTTACTTTTTCATTTCTAAACCTTTTGAAGTATGGTACAATTAAAGTTATGACAAAAGAATTTCATCACGTG
ACCGTACTCCTTCACGAAACAGTGGACATGCTTGACATAAAGCCTGATGGGATTTATGTTGATGCGACGCTAGGTGGCTCAGGC
CACTCAGCTTATTTGTTGTCCAAACTTGGTGAAGAAGGGCACCTCTATTGTTTTGACCAAGACCAAAAGGCTATTGACAATGCAC
AAGTTACCCTCAAATCTTATATTGACAAAGGACAGGTAACTTTTATTAAAGATAATTTTAGACACCTCAAAGCACGTTTAACAGCG
CTTGGAGTTGATGAAATTGATGGTATCTTATATGACCTTGGTGTTTCCAGCCCGCAATTGGATGAAAGAGAACGAGGGTTTTCTT
ATAAACAAGATGCTCCATTGGATATGCGCATGGATCGTCAGTCGCTCTTAACAGCTTACGAAGTGGTGAATACCTATCCATTCAA
TGATTTGGTTAAGATTTTTTTCAAATATGGTGAAGATAAATTCTCCAAGCAGATCGCTCGAAAAATTGAACAAGCAAGAGCTATTA
AGCCTATTGAGACAACAACAGAGTTGGCAGAATTGATTAAGGCAGCAAAGCCAGCTAAAGAGTTGAAGAAAAAAGGCCACCCT
GCTAAACAGATTTTTCAAGCTATTCGCATTGAAGTCAATGATGAATTGGGAGCGGCCGATGAATCTATTCAGGACGCTATGGAAT
TATTAGCCCTTGATGGTCGTATCTCAGTTATTACCTTCCATTCTCTGGAAGATCGCCTAACCAAGCAGTTGTTTAAAGAAGCTAG

TACGGTGGATGTGCCAAAAGGGCTTCCTCTAATTCCTGAAGATATGAAACCTAAGTTTGAACTTGTTTCACGTAAGCCGATCTTA
CCTAGTCATTCAGAGTTAACAGCTAATAAAAGGGCACACTCAGCCAAGCTACGTGTTGCCAAAAAAATTCGGAAATAA

SPy1727
Seq ID 71
GTGACAACGACGGAACAAGAACTTACCTTGACTCCCTTACGTGGGAAAAGTGGCAAAGCTTATAAAGGCACTTATCCAAATGGG
GAATGTGTCTTTATAAAATTAAATACGACCCCTATTCTACCTGCCTTAGCAAAAGAACAGATTGCGCCACAGTTACTTTGGGCCA
AACGCATGGGCAATGGTGATATGATGAGTGCCCAAGAATGGCTTAACGGCCGTACATTGACCAAAGAAGATATGAACAGTAAG
CAAATCATTCATATTCTATTGCGCCTTCACAAATCTAAAAAATTAGTCAATCAACTGCTTCAGCTCAATTATAAGATTGAAAACCCA
TACGATTTATTGGTTGATTTTGAGCAAAATGCACCCTTGCAAATTCAGCAAAATTCATACTTACAAGCTATCGTTAAAGAATTAAA
ACGGAGCTTACCAGAGTTCAAATCAGAAGTAGCAACGATTGTGCATGGAGATATTAAACATAGCAATTGGGTGATTACTACTAGT
GGTATGATTTTTTTAGTAGATTGGGATTCTGTTCGTCTAACTGATCGGATGTATGATGTTGCTTACCTGTTGAGCCACTATATTCC
ACGGTCTCGTTGGTCAGAATGGCTGTCTTATTATGGCTATAAAAATAATGACAAGGTTATGCAAAAAATTATTTGGTATGGTCAAT
TTTCTCACCTGACACAAATTCTCAAGTGTTTTGACAAGCGTGACATGGAGCATGTGAATCAGGAGATTTATGCCCTCAGAAAATT
TAGAGAAATATTTAGAAAGAAATAA

SPy1785
Seq ID 72
ATGATATTAACAGCTCCTATGTCCAACTTAAAGGGATTTGGACCAAAATCAGCAGAAAAATTTCAGAAATTAGATATTTATACAGT
AGAAGATTTACTGCTTTATTATCCGTTTCGCTATGAAGATTTTAAATCAAAATCTGTTTTTGATTTAGTGGATGGTGAAAAAGCAG
TCATTACAGGCTTAGTCGTTACTCCAGCTAATGTACAATATTATGGTTTTAAACGTAACCGTTTAAGTTTCAAATTGCGTCAAGGG
GAAGCTGTCTTAAATGTTAGTTTTTTTAATCAACCCTATTTAGCTGATAAAATAGAACTTGGTCAAGAGGTAGCTGTTTTTGGTAA
ATGGGATGCCACTAAATCGGCTATTACTGGGATGAAGGTTTTAGCTCAAGTTGAAGATGACATGCAACCTGTTTATCGCGTAGC
TCAGGGAATTTCACAGTCTACTTTGATTAAAGCTATTAAGTCAGCTTTTGAAATCGATGCGCATTTGGAATTGAAGGAAAATTTAC
CAGCTACTTTATTGGAAAAATACCGATTGATGGGTCGTAGTCAGGCTTGTTTAGCTATGCATTTCCCAAAAGATATCACAGAGTA
TAAGCAAGCGCTCCGTCGGATTAAATTTGAAGAATTATTTTACTTTCAAATGAACCTTCAAGTTTTGAAAGCCGAAAATAAATCTG
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AAGCGCTCTTTAGATGACATATTATCTGATATGTCATCGGGAGCTCATATGAATCGTTTATTGCAAGGAGATGTAGGATCAGGAA
AGACAGTCATTGCTGGTCTATCAATGTATGCAGCTTATACAGCAGGTTTTCAATCGGCTTTGATGGTTCCAACGGAAATCCTAGC
TGAACAACACTACATTAGTCTGCAAGAGTTATTTCCAGATTTATCAATCGCTATATTAACTTCGGGTATGAAAGCAGCTGTCAAG
CGTACGGTTTTAGCAGCTATTGCAAATGGCTCGGTTGATATGATTGTAGGAACTCATGCTCTTATCCAAGACTCGGTACAGTACC
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ACGATCATGATTATTATGGATGCCGATCGTTTTGGATTAAGTCAGTTACATCAACTTCGTGGGCGTGTTGGTCGTGGATATAAAC
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CGTTTTAGCTGAGTCGGATTTAAAAATGCGTGGTTCTGGTGAAATCTTTGGTACTCGTCAGTCTGGAATTCCAGAATTTCAAGTA
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AAAAACAGTGGCAATTAGTGGCACAAAATATTAGAAAAAAAGAAGTTTATGATTAA

SPy1798
Seq ID 73
ATGAAAAAAATCAGCAAATGTGCGTTTGTGGCAATATCTGCCCTTGTTCTCATTCAGGCTACTCAAACTGTAAAATCACAAGAGC
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ATTGCAGGTCTATCTAGCTTTATGATCGTAGCTCTGGGATTCATTATTGGTCGAAAGACATTATTTAAATAA

SPy1801
Seq ID 74
ATGAATAAAAACAAACTATTAAGAGTTGCCATGCTACTAAGTCTCTTAGCCCCGACAGCAGAAAGCATGACAGTGCTGGCTCAA
GATGTAATGCTTGAGACGCATAAAGCAACTACAAATGAAACCAGTGATTCTTCTTCAAAAGAGGAAAATAATAAAAATGCAGCAC
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SPy1813
Seq ID 75
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CAGAGAATAGCAAAAAAGAATTTAAAGAAGAACTCTCAAAAGCGGGGCAAGAATCTCAAAAGGTCAAAGAGATATTAGCAAAAG
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CTGCTAAAAAAATAA

SPy1821

Seq ID 76
ATGATTGAAGCAAGTAAGCTTAAAGCAGGTATGACATTTGAAGCAGAAGGAAAATTAATCCGTGTCCTTGAAGCTAGCCACCAC
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CCAATTTTATGGAAGTGAAGTGATTGGGGTAACGGTTCCAACAACTGTTGAATTGACCGTTGCGGAAACACAACCATCTATTAAA
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SPy1916
Seq ID 77
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TGTCGATTTGAAACTTAGTGAAGAATTTGGTGTCAACGGCATCCGTATCTCTATTGCCTGGTCTCGTATTTTTCCAACAGGAAAA
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TTTCATGGTCAAATGGCTATGAAAAACGTTACGGTCTCTTCTATGTTGATTTTGAAACTCAAGAACGTTATCCTAAGAAGAGTGC
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SPy1972
Seq ID 78
ATGAAAAAGAAAGTCAACCAAGGATCAAAGCGCTATCAATATCTGTTAAAAAAGTGGGGGATAGGTTTTGTAATCGCTGCAACTG
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CAGCTAATCCTGCTAGTATTGCTGAGCATCATTTGCGTATGCATTTTAAAACATTGCCAGCTGGTGAGTCGCTAGGAAGCTTGG
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SPy1979
Seq ID 79

ATGAAAAATTACTTATCTATTGGAGTGATTGCACTGCTGTTTGCATTAACATTTGGAACAGTCAAGTCGGTCCAAGCTATTGCTG
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AACAGCTAGCGAACGTAACTTAGACTTCAGAGATTTATACGATCCTCGTGATAAGGCTAAACTACTCTACAACAATCTCGATGCT
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AGCGCCCTAAAGGGGCAAAGGGTAGCTATCATTTAGCTTATGATAAAGATCTCTATACCGAAGAAGAACGAAAAGCTTACAGCT
ACCTGCGTGATACAGGGACACCTATACCTGATAACCCTAAAGACAAATAA

SPy1983
Seq ID 80
ATGTTGACATCAAAGCACCATAATCTCAACAAACTAGTCTGGCGCTACGGGCTAACCTCAGCCGCTGCCGTCCTTCTAGCCTTT
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CAGGCCAACCAGGCGAAAAAGCTCCAGAAAAGAGCCCAGAAGGCGAAGCAGGCCAACCAGGCGAAAAAGCTCCAGAAAAGAG
CAAAGAGGTAACTCCAGCTGCAGAAAAACCTGCTGACAAAGAAGCTAACCAAACGCCAGAACGCCGCAATGGCAATATGGCTA
AGACACCTGTAGCCAACAACCACAGACGTCTACCAGCAACTGGTGAGCAAGCCAACCCATTCTTTACAGCAGCAGCAGTAGCA
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SPy1991
Seq ID 81
ATGATACTCTTAATTGATAATTACGATTCATTTACCTACAACCTCGCCCAATATTTAAGTGAATTTGACGAGACGATTGTCTTGTAT
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AACCAAATGCCAAAACTCATTCAAGACTTTTACCAAACAAAACCTATCTTAGGAGTGTGTCTGGGACACCAAGCTATCGCTGAAA
CTTTAGGGGGAACCTTACGCTTGGCCAAACGCGTCATGCATGGGAGACAAAGCACCATTGAAACGCAAGGCCCTGCTAGTCTT
TTTCGCTCCCTGCCACAAGAGATCACCGTCATGCGCTACCATTCCATCGTTGTGGATCAGTTACCAAAAGGTTTTAGCGTAACC
GCTAGAGACTGTGACGATCAAGAAATCATGGCATTTGAACACCACACCCTGCCACTTTTTGGGCTACAATTTCACCCAGAAAGC
ATCGGAACTCCTGATGGCATGACCATGATTGCCAACTTCATCGCAGCCATTCCCCGTTAA

SPy2000
Seq ID 82
GTGTCAAAATACCTAAAATACTTCTCTATTATCACGTTATTTTTGACTGGGCTTATTTTAGTTGCATGTCAACAACAAAAGCCTCAA
ACAAAAGAACGTCAGCGCAAACAACGTCCAAAAGACGAACTTGTCGTTTCTATGGGGGCAAAGCTCCCTCATGAATTCGATCCA
AAGGACCGTTATGGAGTCCACAATGAAGGGAATATCACTCATAGCACTCTATTGAAACGTTCTCCTGAACTAGATATAAAAGGAG
AGCTTGCTAAAACATACCATCTCTCTGAAGATGGGCTGACTTGGTCGTTTGACTTGCATGATGATTTTAAATTCTCAAATGGTGA
GCCTGTTACTGCTGATGATGTTAAGTTTACTTATGATATGTTGAAAGCAGATGGAAAGGCTTGGGATCTAACCTTCATTAAGAAC
GTTGAAGTAGTTGGGAAAAATCAGGTCAATATCCATTTGACTGAGGCGCATTCGACATTTACAGCACAGTTGACTGAAATCCCAA
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AGAACAAGCTATTTTTGTTCGTAACCCTTATTGGCATGGGAAAAAACCATACTTTAAAAAATGGACTTGGGTCTTACTTGATGAAA
ACACAGCACTAGCAGCTTTAGAATCTGGTGATGTTGATATGATCTACGCAACGCCAGAACTTGCTGATAAAAAAGTCAAAGGCA
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TGGTTATCCTGTAGGAAATGATGTCACTAGTGATCCAGCAATCCGAAAAGCCTTGACTATTGGTTTAAATAGGCAAAAAGTTCTC
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TAATAAAGTAGCTAAAGCTAAGCAATTATTGACAAAAGCGGGATGGAAAGAACAAGCAGACGGTAGCCGTAAAAAAGGTGACCT
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CCTAGGGATTACTATTAAACTCAAAGCTAGTAACTGGGATGAAATGGCAACGAAGTCACATGACTCAGCCTTACTTTATGCCGG
AGGACGTCATCACGCGCAGCAATTTTATGAATCGCATCATCCAAGCCTAGCAGGGAAAGGTTGGACCAATATTACGTTTTATAA
CAATCCTACCGTGACTAAGTACCTTGACAAAGCAATGACATCTTCTGACCTTGATAAAGCTAACGAATATTGGAAGTTAGCGCAG
TGGGATGGCAAAACAGGTGCTTCTACTCTTGGAGATTTGCCAAATGTATGGTTGGTGAGCCTTAACCATACTTATATTGGTGATA
AACGTATCAATGTAGGTAAACAAGGCGTCCACAGTCATGGTCATGATTGGTCATTATTGACTAACATTGCCGAGTGGACTTGGG
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SPy2006
Seq ID 83
GTGAAGAAAACATATGGTTATATCGGCTCAGTTGCTGCTATTTTACTAGCTACTCATATTGGAAGTTACCAACTTGGTAAGCATC
ATATGGGTTCAGCAACAAAGGACAATCAAATTGCCTATATTGATGATAGCAAAGGTAAGGCAAAAGCCCCTAAAACAAACAAAAC
GATGGATCAAATCAGTGCTGAAGAAGGCATCTCTGCTGAACAGATCGTAGTCAAAATTACTGACCAAGGCTATGTGACCTCACA
TGGTGACCATTATCATTTTTACAATGGGAAAGTTCCTTATGATGCGATTATTAGTGAAGAGTTGTTGATGACGGATCCTAATTACC
GTTTTAAACAATCAGACGTTATCAATGAAATCTTAGACGGTTACGTTATTAAAGTCAATGGCAACTATTATGTTTACCTCAAGCCA
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AAAAAGGATTTGTCTCCAAGTGAGCTAGCTGCTGCACAAGCCTACTGGAGTCAAAAACAAGGTCGAGGTGCTAGACCGTCTGAT
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TCAGATAAAGAAGTGACACATACCTTTCTTGGTCATCGCATCAAAGCTTACGGAAAAGGCTTAGATGGTAAACCATATGATACGA
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ATATCGATCCTAAGTATCTCATTTTCCAACCAGAAGGTGTCCAATTTTATAATAAAAATGGTGAATTGGTAACTTATGATATCAAG
ACACTTCAACAAATAAACCCTTAA

SPy2009
Seq ID 84
ATGCGTAGAGCAGAAAATAACAAACACAGCCGCTATTCCATTCGCAAACTGAGCGTTGGGGTAACGAGTATAGCAATTGCGAGT
CTCTTTTTAGGAAAGGTTGCCTATGCCGTAGATGGCATCCCTCCAATCTCTCTTACTCAAAAGACTACAGCCACTACATCAGAAA
ATTGGCATCATATTGATAAGGATGGCCTTATTCCTTTAGGTATAAGCTTAGAAGCTGCCAAAGAGGAATTTAAAAAAGAAGTAGA
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CGGAAAGTCCAGTGGCCCCAGCTTTATCTGAGGCTCCAGCTCAACCAGCTGAGAGTGAGGAACCTTCAGTAGCAGCATCTTCT
GAGGAAACCCCATCTCCATCAACTCCAGCGGCCCCAGAAACTCCTGAAGAACCAGCAGCTCCATCTCCATCACCTGAGAGTGA
GGAACCTTCAGTAGCAGCTCCTTCTGAGGAAACCCCATCTCCAGAAACTCCTGAAGAACCAGCAGCTCCATCTCAACCAGCTGA
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AACTTCAAAGAGATCTTCTGATAAAAAAGAAGAGCAAGAACAGTCTTACTCTCCAAATCGCTCATTGTCAAGACAGGTTAGGGCC
CATGAGTCAGGTAAGTACTTGCCTTCAACAGGTGAAAAAGCACAGCCACTCTTTATAGCTACTATGACTTTGATGTCTCTATTTG
GCAGTCTTTTAGTCACAAAACGCCAAAAAGAAACTAAAAAATAG

SPy2010
Seq ID 85
TTGCGTAAAAAACAAAAATTACCATTTGATAAACTTGCCATTGCGCTCATGTCTACGAGCATCTTGCTCAATGCACAATCAGACAT
TAAAGCAAATACTGTGACAGAAGACACTCCTGCTACCGAACAAGCTGTAGAAACCCCACAACCAACAGCGGTTTCTGAGGAAGC
ACCATCATCAAAGGAAACCAAAACCCCACAAACTCCTGATGACGCAGAAGAAACAATAGCAGATGACGCTAATGATCTAGCCCC
TCAAGCTCCTGCTAAAACTGCTGATACACCAGCAACCTCAAAAGCGACTATTAGGGATTTGAACGACCCTTCTCAGGTCAAAAC
CCTGCAGGAAAAAGCAGGCAAAGGAGCTGGGACTGTTGTTGCAGTGATTGATGCTGGTTTTGATAAAAATCATGAAGCGTGGC
GCTTAACAGACAAAACCAAAGCACGTTACCAATCAAAAGAAGATCTTGAAAAAGCTAAAAAAGAGCACGGTATTACCTATGGCG
AGTGGGTCAATGATAAGGTTGCTTATTACCACGACTATAGTAAAGATGGTAAAACCGCTGTCGATCAAGAGCACGGCACACACG
TGTCAGGGATCTTGTCAGGAAATGCTCCATCTGAAACGAAAGAACCTTACCGCCTAGAAGGTGCGATGCCTGAGGCTCAATTG
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TGCCAAATCAAAAGGTGTTAGCATTGTGACCTCAGCTGGTAATGATAGTAGCTTTGGGGGCAAGACCCGTCTACCTCTAGCAGA
TCATCCTGATTATGGGGTGGTTGGGACACCTGCAGCGGCAGACTCAACATTGACAGTTGCTTCTTACAGCCCAGATAAACAGCT
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GGCTTACGACTATGCTTATGCTAATCGTGGGATGAAAGAGGATGATTTTAAGGATGTCAAAGGTAAGATTGCCCTTATTGAACGT
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AGCTTATTTTTCTCCTCGCCAACAAGGAGCAGGAGCAGTCGATGCTAAAAAAGCTTCAGCAGCAACGATGTATGTGACAGATAA
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TCCCTATATTGGTTTCCGAGGTGATTTTGGCAATCTGTCAGCCTTAGAAAAACCAATCTATGATAGCAAAGACGGTAGCAGCTAC
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TATGCTGCGATCTCTCCAAATGGGGACGGTAACAGAGATTATGTCCAATTCCAAGGTACTTTCTTGCGTAATGCTAAAAACCTTG
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GGTTTACCGTGAGCGTATTGCTTACACTTATATGGATGAGGATCTGCCAACAACAGAGTATATTTCTCCAAATGAAGATGGTACC
TTTACTCTTCCTGAAGAGGCTGAAACAATGGAAGGCGCTACTGTTCCATTGAAAATGTCAGACTTTACTTATGTTGTTGAAGATA
TGGCTGGTAACATCACTTATACACCAGTGACTAAGCTATTGGAAGGCCACTCTAATAAACCAGAACAAGACGGTTCAGATCAAG
CACCAGACAAAAAACCAGAAACTAAACCAGAACAAGACGGTTCAGGTCAAGCACCAGATAAAAAACCAGAAACTAAACCAGAAC
AAGACGGTTCAGGTCAAACACCAGACAAAAAACCAGAAACTAAACCAGAACAAGACGGTTCAGGTCAAACACCAGATAAAAAAC
CAGAAACTAAACCAGAAAAAGATAGTTCAGGTCAAACACCAGGTAAAACTCCTCAAAAAGGTCAACCTTCTCGTACTCTAGAGAA
ACGATCTTCTAAGCGTGCTTTAGCTACAAAAGCATCAACAAAAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGTTTA
CATCTCCTTAAGTTAGTTATGACCACTTTCTTCTTGGGATTAGTAGCTCATATCTTTAAAACAAAACGCACTGAAGATTAG

SPy2016
Seq ID 86
ATGAATATTAGAAATAAGATTGAAAATAGTAAAACACTACTATTTACATCCCTTGTAGCCGTGGCTCTACTAGGAGCTACACAACC
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TAAAGAAGAATGGCCTGAAGATTGGCCTGAAGATGACTGGTCTAGCGATAAAAAAGATGAGACAGAAGATAAAACGAGACCACC
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CACCATATGGAGGAGCATTAGGTACAGGGTATGAAAAACGTGATGATTGGGGAGGACCTGGTACGGTGGCAACTGACCCTTAC
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AAAAATCCACAAGAATCAGATTTTGATAGAGGGTTTTCAGCTGGCTTGAAAGCAAAAAACTCAGGTAGAGGTATTGATTTTGAAG
GTTTCCAGTATGGTGGCTGGTCAGACGAATATAAAAAAGGTTACATGCAAGCCTTCGGTACACCATATACACCATCAGCAACGT
AA

SPy2018
Seq ID 87
ATGGCTAAAAATAACACGAATAGACACTATTCGCTTAGAAAATTAAAAACAGGAACGGCTTCAGTAGCGGTAGCTTTGACTGTTT
TAGGGGCAGGTTTTGCGAATCAAACAGAGGTTAAGGCTAACGGTGATGGTAATCCTAGGGAAGTTATAGAAGATCTTGCAGCAA
ACAATCCCGCAATACAAAATATACGTTTACGTTACGAAAACAAGGACTTAAAAGCGAGATTAGAGAATGCAATGGAAGTTGCAG
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AGAACTACAACAAGACTATGACTTAGCAAAGGAATCAACAAGTTGGGATAGACAAAGACTTGAAAAAGAGTTAGAAGAGAAAAA
GGAAGCTCTTGAATTAGCGATAGACCAGGCAAGTCGGGACTACCATAGAGCTACCGCTTTAGAAAAAGAGTTAGAAGAGAAAAA
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AAGCCGTCAAGGCCTTCGCCGTGACTTGGACGCATCACGTGAAGCTAAGAAACAGGTTGAAAAAGATTTAGCAAACTTGACTGC
TGAACTTGATAAGGTTAAAGAAGAAAAACAAATCTCAGACGCAAGCCGTCAAGGCCTTCGCCGTGACTTGGACGCATCACGTGA
AGCTAAGAAACAAGTTGAAAAAGCTTTAGAAGAAGCAAACAGCAAATTAGCTGCTCTTGAAAAACTTAACAAAGAGCTTGAAGAA
AGCAAGAAATTAACAGAAAAAGAAAAAGCTGAACTACAAGCAAAACTTGAAGCAGAAGCAAAAGCACTCAAAGAACAATTAGCG
AAACAAGCTGAAGAACTTGCAAAACTAAGAGCTGGAAAAGCATCAGACTCACAAACCCCTGATACAAAACCAGGAAACAAAGCT
GTTCCAGGTAAAGGTCAAGCACCACAAGCAGGTACAAAACCTAACCAAAACAAAGCACCAATGAAGGAAACTAAGAGACAGTTA
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AAACGCAAAGAAGAAAACTAA

SPy2025
Seq ID 88
ATGAAGAAAAGGAAATTGTTAGCAGTAACACTATTAAGTACCATACTCTTAAACAGTGCAGTGCCATTAGTTGTTGCTGATACCT
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ACAAAAAAAGCAAGGAAACAGCGTCGCAGCACGACACCCAAAAAGACCATAAGCCATCACACACTCACCCAACCCCCCCTTCA
AATGATACTAAGCAGACCGATCAGGCATCATCTGAAGCTACTGACAAACCAAATAAAGACAAAAACGACACCAAGCAACCAGAC
AGCAGTGATCAATCCACCCCATCTCCCAAAGACCAGTCGTCTCAAAAAGAGTCACAAAACAAAGACGGCCGACCTACCCCATCA
CCTGATCAGCAAAAAGATCAGACACCTGATAAAACACCAGAAAAATCAGCTGATAAAACCCCTGAAAAAGGACCAGAAAAAGCA
ACTGATAAAACACCAGAGCCAAATCGTGACGCTCCAAAACCCATCCAACCTCCTTTAGCAGCTGCTCCTGTCTTTATACCTTGGA
GAGAAAGTGACAAAGACCTGAGCAAGCTAAAACCAAGCAGTCGCTCATCAGCGGCTTACGTGAGACACTGGACAGGTGACTCT
GCCTACACTCACAACCTGTTGTCACGCCGTTATGGGATTACTGCTGAACAGCTAGATGGTTTTTTGAACAGTCTAGGTATTCACT
ATGATAAAGAACGCTTAAACGGAAAGCGTTTATTAGAATGGGAAAAACTAACAGGACTAGACGTTCGAGCTATCGTAGCTATTG
CAATGGCAGAAAGCTCACTAGGTACTCAGGGAGTTGCTAAAGAAAAAGGAGCCAATATGTTTGGTTATGGCGCCTTTGACTTCA
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CCTTTGAAAGACAAGACCTCAAAGCAAAAAAATGGTCACTAGGCCAGTTGGATACCTTGATTGATGGTGGGGTTTACTTTACAG
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TGACCTACAAGTCAGAGACCTACAGCTTTGGCCAATGCACTTGGTACGCCTATAATCGTGTCAAAGAGCTAGGTTATCAAGTCG
ACAGGTACATGGGTAACGGTGGCGACTGGCAGCGCAAGCCAGGTTTTGTGACCACCCATAAACCTAAAGTGGGCTATGTCGTC
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TTAATTTCAGAGTCAAATGTTATGGGACTAGGCACCATTTCCTATCGGACGTTCACAGCTGAGCAGGCTAGTTTGTTGACCTATG
TCGTAGGGGACAAACTCCCAAGACCATAA

SPy2039
Seq ID 89
ATGAATAAAAAGAAATTAGGTGTCAGATTATTAAGTCTTTTAGCATTAGGTGGATTTGTTCTTGCTAACCCAGTATTTGCCGATCA
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AGCGCAGAAGATATTAAGCTTGACAAAGTTAACTTAGGTGGAGAACTTTCTGGCTCTAATATGTATGTTTACAATATTTCTACTGG
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GAAAACATTGCTTCCTTCATGGAAAGTTATGTCGAACAAATCAAAGAAAACAAAAAATTAGACACTACTTATGCTGGTACCGCTG
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AAAAAATGGCGATTTCAGAATTGATGGCTGATGTTGGTATTTCAGTAGACATGGATTATGGTCCATCTAGTGGTTCTGCAGGTAG
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ACCTTAG

SPy2043
Seq ID 90
ATGAATCTACTTGGATCAAGACGGGTTTTTTCTAAAAAATGTCGGCTAGTAAAATTTTCAATGGTAGCTCTTGTATCAGCCACAAT
GGCTGTAACAACAGTCACACTTGAAAATACTGCACTGGCACGACAAACACAGGTCTCAAATGATGTTGTTCTAAATGATGGCGC
AAGCAAGTACCTAAACGAAGCATTAGCTTGGACATTCAATGACAGTCCCAACTATTACAAAACCTTAGGTACTAGTCAGATCACT
CCAGCACTCTTTCCTAAAGCAGGAGATATTCTCTATAGCAAATTAGATGAGTTAGGAAGGACGCGTACTGCTAGAGGTACATTG
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AATCATGTCAAATATAAAATTGAATGGTTAAATGGTCTATCTTATGTCGGAGATTTCTGGAATAGAAGTCATCTCATTGCAGATAG
TCTCGGTGGAGATGCACTCAGAGTCAATGCCGTTACAGGGACACGTACCCAAAATGTAGGAGGTCGTGACCAAAAAGGCGGCA
TGCGCTATACCGAACAAAGAGCTCAAGAATGGTTAGAAGCAAATCGTGATGGCTATCTTTATTATGAAGCTGCTCCAATCTATAA
CGCAGACGAGTTGATTCCAAGAGCTGTCGTGGTATCAATGCAATCTTCTGATAATACCATCAACGAGAAAGTATTAGTTTACAAC
ACAGCTAATGGCTACACCATTAACTACCATAACGGTACACCTACTCAGAAATAA

SPy2059
Seq ID 91
ATGAGATTTCTAGAACTTTTACAAAAGAAATTTTTTCCTAAAGCATATCAGGAAAAACAATTCTTAATGCATCAAAAAACGCGTTTA
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GCAACAGCTCTGCAACGCAGTAGAGCCTACGAAGGAAGCCCTAAAAGTCGGCCCGCTTGGTTGCAAAAGCTGGAAGCTGTTTT
GCCGTCTCCTCAACGTCCAATTCGGCGTTTTTGGCGCCGCTATCACATCGGAAAACTGCTAATGATTCTGATTGGAACTCTTGT
CTTACTCTTAGGATCATACTTGTTTTACTTATCAAAAACAGCTAAAGTATCTGATTTACAAGATGCCTTGAAGGCTACAACGGTTA
TTTATGATCACAAAGGAGAGTATGCAGGCAGTTTATCTGGTCAAAAAGGGAGTTATGTTGAGCTCAACGCTATTTCAGATGATCT
TGAGAATGCTGTTATTGCCACTGAGGATAGGACTTTTTACAGTAATAGCGGTATTAATCTTAAACGCTTCTTATTGGCGGTAGTT
ACGGCGGGCCGCTTTGGAGGTGGCTCAACGATTACACAGCAACTGGCTAAAAATGCTTATCTCTCACAAGATCAGACAATTAAA
CGAAAGGCCCGAGAGTTTTTTTTGGCGTTAGAGTTGACCAAAAAATACAGTAAAAAAGATATTCTTACTATGTACCTTAACAACTC
CTACTTTGGAAATGGAGTTTGGGGAGTTGAAGATGCCAGTCAAAAATATTTTGGAACCACAGCTGCTAACTTAACACTGGATGAA
GCTGCCACATTAGCAGGTATGCTCAAAGGACCTGAAATATATAACCCTTACCATTCTCTAAAAAATGCTACTCACCGTAGAGATA
CTGTTTTAGGAGCGATGGTTGATGCCAAAAAGATTACCCAAACAAAAGCTCAGCAAGCTAGAGCAGTAGGGCTAAAAAATCGCT
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SPy0019
Seq ID 152
MKKRILSAVLVSGVTLGAATTVGAEDLSTKIAKQDSIISNLTTEQKAAQNQVSALQAQVSSLQSEQDKLTARNTELEALSKRFEQEIKAL
TSQIVARNEKLKNQARSAYKNNETSGYINALLNSKSISDVVNRLVAINRAVSANAKLLEQQKADKVSLEEKQAANQTAINTIAANMAMA
EENQNTLRTQQANLVAATANLALQLASATEDKANLVAQKEAAEKAAAEALAQEQAAKVKAQEQAAQQAASVEAAKSAITPAPQATPA
AQSSNAIEPAALTAPAAPSAGPQTSYDSSNTYPVGQCTWGAKSLAPWAGNNWGNGGQWAYSAQAAGYRTGSTPMVGAIAVWND
GGYGHVAVVEVQSASSIRVMESNYSGRQYIADHRGWFNPTGVTFIYPH

SPy0025
Seq ID 153
MSSYFPVAPLSDLVSYMNKRIFVEKKADFGIKSASLVKELTHNLQLTSLKALRIVQVYDVFNLAEDLLARAEKHIFSEQVTDCLLTETEIT
AELDKVAFFAIEALPGQFDQRAASSQEALLLFGSDSQVKVNTAQLYLVNKDITEAELEAVKNYLLNPVDSRFKDITLPLEEQAFSVSDK
TIPNLDFFETYQADDFATYKAEQGLAMEVDDLLFIQNYFKSIGCVPTETELKVLDTYWSDHCRHTTFETELKNIDFSASKFQKQLQTTY
DKYIAMRDELGRSEKPQTLMDMATIFGRYERANGRLDDMEVSDEINACSVEIEVDVDGVKEPWLLMFKNETHNHPTEIEPFGGAATCI
GGAIRDPLSGRSYVYQAMRISGAGDITTPIAETRAGKLPQQVISKTAAHGYSSYGNQIGLATTYVREYFHPGFVAKRMELGAVVGAAP
KENVVREKPEAGDVVILLGGKTGRDGVGGATGSSKVQTVESVETAGAEVQKGNAIEERKIQRLFRDGNVTRLIKKSNDFGAGGVCVA
IGELADGLEIDLDKVPLKYQGLNGTEIAISESQERMSVVVRPNDVDAFIAACNKENIDAVVVATVTEKPNLVMTWNGEIIVDLERRFLDT
NGVRVVVDAKVVDKDLTVPEARTTSAETLEADTLKVLSDLNHASQKGLQTIFDSSVGRSTVNHPIGGRYQITPTESSVQKLPVQHGVT
TTASVMAQGYNPYIAEWSPYHGAAYAVIEATARLVATGADWSRARFSYQEYFERMDKQAERFGQPVSALLGSIEAQIQLGLPSIGGK
DSMSGTFEDLTVPPTLVAFGVTTADSRKVLSPEFKAAGENIYYIPGQAISEDIDFDLIKDNFSQFEAIQAQHKITAASAAKYGGVLESLAL
MTFGNRIGASVEIAELDSSLTAQLGGFVFTSAEEIADAVKIGQTQADFTVTVNGNDLAGASLLAAFEGKLEEVYPTEFEQTDVLEEVPA
VVSDTVIKAKETIEKPVVYIPVFPGTNSEYDSAKAFEQVGASVNLVPFVTLNEVAIAESVDTMVANIAKANIIFFAGGFSAADEPDGSAKF
IVNILLNEKVRAAIDSFIEKGGLIIGICNGFQALVKSGLLPYGNFEEAGETSPTLFYNDANQHVAKMVETRIANTNSPWLAGVEVGDIHAI
PVSHGEGKLVVSASEFAELRDNGQIWSQYVDFDGQPSMDSKYNPNGSVNAIEGITSKNGQIIGKMGHSERWEDGLFQNIPGNKDQIL
FASAVKYFTGK

SPy0031
Seq ID 154
MKKFHRFLVSGVILLGFNGLVPTMPSTLISQQENLVHAAVLGDNYPSKWKKGNGIDSWNMYIRQCTSFAAFRLSSANGFQLPKGYGN
ACTWGHIAKNQGYPVNKTPSIGAIAWFDKNAYQSNAAYGHVAWVADIRGDTVTIEEYNYNAGQGPERYHKRQIPKSQVSGYIHFKDL
SSQTSHSYPRQLKHISQASFDPSGTYHFTTRLPVKGQTSIDSPDLAYYEAGQSVYYDKVVTAGGYTWLSYLSFSGNRRYIPIKEPAQS
VVQNDNTKPSIKVGDTVTFPGVFRVDQLVNNLIVNKELAGGDPTPLNWIDPTPLDETDNQGKVLGDQILRVGEYFIVTGSYKVLKIDQP
SNGIYVQIGSRGTWVNADKANKL

SPy0103
Seq ID 155
MINQWNNLRHKKLKGFTLLEMLLVILVISVLMLLFVPNLSKQKDRVTETGNAAVVKLVENQAELYELSQGSKPSLSQLKADGSITEKQE
KAYQDYYDKHKNEKARLSN

SPy0112
Seq ID 156
MKIGIIGVGKMASAIIKGLKQTPHELIISGSSLERSKEIAEQLALPYAMSHQDLIDQVDLVILGIKPQLFETVLKPLHFKQPIISMAAGISLQR
LATFVGQDLPLLRIMPNMNAQILQSSTALTGNALVSQELQARVRDLTDSFGSTFDISEKDFDTFTALAGSSPAYIYLFIEALAKAGVKNG
IPKAKALEIVTQTVLASASNLKTSSQSPHDFIDAICSPGGTTIAGLMELERLGLTATVSSAIDKTIDKAKSL

SPy0115
Seq ID 157
MTDLFSKIKEVTELDGIAGYEHSVRDYLRTKITPLVDRVETDGLGGIFGIRDSKAEKAPRILVAAHMDEVGFMVSDIKVDGTLRVVGIGG
WNPLVVSSQRFTLYTRTGQVIPLISGSVPPHFLRGANGSASLPHIEDIVFDGGFTDKAEAERFGITPGDIIIPQSETILTANQKNIISKAWD
NRYGVLMITEMLEALKGQDLNNTLIAGANVQEEVGLRGAHVSTTKFDPELFFAVDCSPAGDIYGNPGTIGDGTLLRFYDPGHVMLKD
MRDFLLTTAEEAGVNFQYYCGKGGTDAGAAHLQNGGVPSTTIGVCARYIHSHQTLYAMDDFVEAQAFLQAIIKKLDRSTVDLIKCY

SPy0166
Seq ID 158
MEDISDPEVILEYGVYPAFIKGYTQLKANIEEALLEMSNSGQALDIYQAVQTLNAENMLLNYYESLPFYLNRQSILANMTKALKDAHIRE
AMAHYKLGEFAHYQDTMLDMVERTIKTF

SPy0167

Seq ID 159
MSNKKTFKKYSRVAGLLTAALIIGNLVTANAESNKQNTASTETTTTNEQPKPESSELTTEKAGQKTDDMLNSNDMIKLAPKEMPLESA
EKEEKKSEDKKKSEEDHTEEINDKIYSLNYNELEVLAKNGETIENFVPKEGVKKADKFIVIERKKKNINTTPVDISIIDSVTDRTYPAALQL
ANKGFTENKPDAVVTKRNPQKIHIDLPGMGDKATVEVNDPTYANVSTAIDNLVNQWHDNYSGGNTLPARTQYTESMVYSKSQIEAAL
NVNSKILDGTLGIDFKSISKGEKKVMIAAYKQIFYTVSANLPNNPADVFDKSVTFKELQRKGVSNEAPPLFVSNVAYGRTVFVKLETSSK
SNDVEAAFSAALKGTDVKTNGKYSDILENSSFTAVVLGGDAAEHNKVVTKDFDVIRNVIKDNATFSRKNPAYPISYTSVFLKNNKIAGV
NNRTEYVETTSTEYTSGKINLSHQGAYVAQYEILWDEINYDDKGKEVITKRRWDNNWYSKTSPFSTVIPLGANSRNIRIMARECTGLA
WEWWRKVIDERDVKLSKEINVNISGSTLSPYGSITYK

SPy0168
Seq ID 160
MKQQSYQPLRFVYLLVALFAALLLIARPVMADEGTNSADAAYYKGQSAGKKAGKKAGKEATWTDLTPTVPTNPETPSDIGETTNKQL
YKEGYKDGYKEGYNEGWKSQYPVLTPVKVIWDLISYWLQRLFPNNQSSTAAQSMS

SPy0171
Seq ID 161
VKNKLFLVALATVTVLGPSLATPHHQTVHASDVTLTETCDKNGTVCFGYENVDGEVCKLTADGKGTICVGYENRDIKESETSSTKNDC
SNWFWCFLNYLWTTIKSWVS

SPy0183
Seq ID 162
METILEVKHLSKIFGKKQKAALEMVKTGKNKSEIFKKTGATVGVYDASFEVKKGEIFVIMGLSGSGKSTLVRMLNRLIEPSAGSILLEGK
DISTMSADQLREVRRHDINMVFQSFALFPHKTILENTEFGLELRGVPKEERQRLAEKALDNSGLLDFKDQYPNQLSGGMQQRVGLAR
ALANSPKILLMDEAFSALDPLIRREMQDELLDLQDSMKQTIIFISHDLNEALRIGDRIALMKDGQIMQIGTGEEILTNPANDFVREFVEDV
DRSKVLTAQNIMIKPLTTTVELDGPQVALNRMHNEEVSMLMATNRRRQLVGSLTADAAIEARKKGLPLSEVIDRDVRTVSKDTIITDILP
LIYDSSAPIAVTDDNNRLLGVIIRGRVIEALANISDEDLN

SPy0230
Seq ID 163
MKTARFFWFYFKRYRFSFTVIAVAVILATYLQVKAPVFLGESLTELGKIGQAYYVAKMSGQTHFSPDLSAFNAVMFKLLMTYFFTVLAN
LIYSFLLTRVVSHSTNRMRKGLFGKLERLTVAFFDRHKDGEILSRFTSDLDNIQNSLNQSLIQVVTNIALYIGLVWMMFRQDSRLALLTIA
STPVALIFLVINIRLARKYTNIQQQEVSALNAFMDETISGQKAIIVQGVQEDTMTAFLKHNERVRQATFKRRLFSGQLFPVMNGMSLINT
AIVIFVGGSTIVLSDKSMPAAAALGLVVTFVQYSQQYYQPMMQIASSWGELQLAFTGAHRIQEMFDETEEVRPQNAPAFTSLKEAVAIN
HVDFGYLPGQKVLSDVSIVAPKGKMIAVVGPTGSGKTTIMNLINRFYDVDAGSITFDGRDIRDYDLDSLRQKVGIVLQESVLFSGTITDN
IRFGDQTISQDMVETAARATHIHDFIMSLPKGYNTYVSDDDNVFSTGQKQLISIARTLLTDPEVLILDEATSNVDTVTESKIQRAMEAIVA
GRTSFVIAHRLKTILNADHIIVLKDGKVIEQGNHHELLHQKGFYAELYHNQFVFE

SPy0269
Seq ID 164
MDLEQTKPNQVKQKIALTSTIALLSASVGVSHQVKADDRASGETKASNTHDDSLPKPETIQEAKATIDAVEKTLSQQKAELTELATALT
KTTAEINHLKEQQDNEQKALTSAQEIYTNTLASSEETLLAQGAEHQRELTATETELHNAQADQHSKETALSEQKASISAETTRAQDLVE
QVKTSEQNIAKLNAMISNPDAITKAAQTANDNTKALSSELEKAKADLENQKAKVKKQLTEELAAQKAALAEKEAELSRLKSSAPSTQDS
IVGNNTMKAPQGYPLEELKKLEASGYIGSASYNNYYKEHADQIIAKASPGNQLNQYQDIPADRNRFVDPDNLTPEVQNELAQFAAHMI
NSVRRQLGLPPVTVTAGSQEFARLLSTSYKKTHGNTRPSFVYGQPGVSGHYGVGPHDKTIIEDSAGASGLIRNDDNMYENIGAFNDV
HTVNGIKRGIYDSIKYMLFTDHLHGNTYGHAINFLRVDKHNPNAPVYLGFSTSNVGSLNEHFVMFPESNIANHQRFNKTPIKAVGSTKD
YAQRVGTVSDTIAAIKGKVSSLENRLSAIHQEADIMAAQAKVSQLQGKLASTLKQSDSLNLQVRQLNDTKGSLRTELLAAKAKQAQLE
ATRDQSLAKLASLKAALHQTEALAEQAAARVTALVAKKAHLQYLRDFKLNPNRLQVIRERIDNTKQDLAKTTSSLLNAQEALAALQAKQ
SSLEATIATTEHQLTLLKTLANEKEYRHLDEDIATVPDLQVAPPLTGVKPLSYSKIDTTPLVQEMVKETKQLLEASARLAAENTSLVAEA
LVGQTSEMVASNAIVSKITSSITQPSSKTSYGSGSSTTSNLISDVDESTQRALKAGVVMLAAVGLTGFRFRKESK

SPy0287
Seq ID 165
MTKEKLVAFSQAHAEPAWLQERRLAALEAIPNLELPTIERVKFHRWNLGDGTLTENESLASVPDFIAIGDNPKLVQVGTQTVLEQLPM
ALIDKGVVFSDFYTALEEIPEVIEAHFGQALAFDEDKLAAYHTAYFNSAAVLYVPDHLEITTPIEAIFLQDSDSDVPFNKHVLVIAGKESKF
TYLERFESIGNATQKISANISVEVIAQAGSQIKFSAIDRLGPSVTTYISRRGRLEKDANIDWALAVMNEGNVIADFDSDLIGQGSQADLKV
VAASSGRQVQGIDTRVTNYGQRTVGHILQHGVILERGTLTFNGIGHILKDAKGADAQQESRVLMLSDQARADANPILLIDENEVTAGH
AASIGQVDPEDMYYLMSRGLDQETAERLVIRGFLGAVIAEIPIPSVRQEIIKVLDEKLLNR

SPy0292
Seq ID 166
MIKRLISLVVIALFFAASTVSGEEYSVTAKHAIAVDLESGKVLYEKDAKEVVPVASVSKLLTTYLVYKEVSKGKLNWDSPVTISNYPYELT
TNYTISNVPLDKRKYTVKELLSALVVNNANSPAIALAEKIGGTEPKFVDKMKKQLRQWGISDAKVVNSTGLTNHFLGANTYPNTEPDD
ENCFCATDLAIIARHLLLEFPEVLKLSSKSSTIFAGQTIYSYNYMLKGMPCYREGVDGLFVGYSKKAGASFVATSVENQMRVITVVLNA
DQSHEDDLAIFKTTNQLLQYLLINFQKVQLIENNKPVKTLYVLDSPEKTVKLVAQNSLFFIKPIHTKTKNTVHITKKSSTMIAPLSKGQVLG
RATLQDKHLIGQGYLDTPPSINLILQKNISKSFFLKVWWNRFVRYVNTSL

SPy0295
Seq ID 167
MESIDKSKFRFVERDSEASEVIDTPAYSYWKSVFRQFFSKKSTVFMLVILVTVLMMSFIYPMFANYDFNDVSNINDFSKRYIWPNAEY
WFGTDKNGQSLFDGVWYGARNSILISVIATLINITIGVVLGAIWGVSKAFDKVMIEIYNIISNIPSMLIIIVLTYSLGAGFWNLILAFCITGWIG
VAYSIRVQILRYRDLEYNLASQTLGTPMYKIAVKNLLPQLVSVIMTMLSQMLPVYVSSEAFLSFFGIGLPTTTPSLGRFIANYSSNLTTNA
YLFWIPLVTLILVSLPLYIVGQNLADASDPRSHR

SPy0348
Seq ID 168
LALTDFKDKDQQDQQRSFKEQILAELEKANQIRKEKEEELFQKELEAKEAARRTAQLYAEYKRQDAFQKESIAHNNKTAKHFQAIKGA

VMTSEALKPTLLSEKENSSLKTTNKRVVQANELQETASKESQVPLTIEKGHSVRRKLSKRQQTERAAKKISTVLISSIIITLLAVTLAGAG
YVYSALNPVDKNSDAFVQVEIPSGSGNKLIGQILQKKGLIKNSTVFSFYTKFKNFTNFQSGYYNLQKSMSLEEIASALQEGGTAEPTKP
SLGKILIPEGYTIKQIAKAVEHNSKGKTKKAKTPFNEKDFLDLVTDEAFIQDMVKRYPKLLATIPTKEKAIYRLEGYLFPATYNYYKETTM
RELVEDMLAAMDATLVPYYDKIAASGKTVNEVLTLASLVEKEGSTDDDRRQIASVFYNRLNSGMALQSNIAILYAMGKLGEKTTLAEDA
TIDTTINSPYNIYTNTGLMPGPVASSGVSAIEATLNPASTDYLYFVANVHTGEVYYAKTFEEHSANVEKYVNSQIQ

SPy0416
Seq ID 169
VEKKQRFSLRKYKSGTFSVLIGSVFLVMTTTVAADELSTMSEPTITNHAQQQAQHLTNTELSSAESKSQDTSQITLKTNREKEQSQDL
VSEPTTTELADTDAASMANTGSDATQKSASLPPVNTDVHDWVKTKGAWDKGYKGQGKVVAVIDTGIDPAHQSMRISDVSTAKVKSK
EDMLARQKAAGINYGSWINDKVVFAHNYVENSDNIKENQFEDFDEDWENFEFDAEAEPKAIKKHKIYRPQSTQAPKETVIKTEETDGS
HDIDWTQTDDDTKYESHGMHVTGIVAGNSKEAAATGERFLGIAPEAQVMFMRVFANDIMGSAESLFIKAIEDAVALGADVINLSLGTA
NGAQLSGSKPLMEAIEKAKKAGVSVVVAAGNERVYGSDHDDPLATNPDYGLVGSPSTGRTPTSVAAINSKWVIQRLMTVKELENRAD
LNHGKAIYSESVDFKDIKDSLGYDKSHQFAYVKESTDAGYNAQDVKGKIALIERDPNKTYDEMIALAKKHGALGVLIFNNKPGQSNRS
MRLTANGMGIPSAFISHEFGKAMSQLNGNGTGSLEFDSVVSKAPSQKGNEMNHFSNWGLTSDGYLKPDITAPGGDIYSTYNDNHYG
SQTGTSMASPQIAGASLLVKQYLEKTQPNLPKEKIADIVKNLLMSNAQIHVNPETKTTTSPRQQGAGLLNIDGAVTSGLYVTGKDNYG
SISLGNITDTMTFDVTVHNLSNKDKTLRYDTELLTDHVDPQKGRFTLTSHSLKTYQGGEVTVPANGKVTVRVTMDVSQFTKELTKQMP
NGYYLEGFVRFRDSQDDQLNRVNIPFVGFKGQFENLAVAEESIYRLKSQGKTGFYFDESGPKDDIYVGKHFTGLVTLGSETNVSTKTI
SDNGLHTLGTFKNADGKFILEKNAQGNPVLAISPNGDNNQDFAAFKGVFLRKYQGLKASVYHASDKEHKNPLWVSPESFKGDKNFN
SDIRFAKSTTLLGTAFSGKSLTGAELPDGHYHYVVSYYPDVVGAKRQEMTFDMILDRQKPVLSQATFDPETNRFKPEPLKDRGLAGV
RKDSVFYLERKDNKPYTVTINDSYKYVSVEDNKTFVERQADGSFILPLDKAKLGDFYYMVEDFAGNVAIAKLGDHLPQTLGKTPIKLKL
TDGNYQTKETLKDNLEMTQSDTGLVTNQAQLAVVHRNQPQSQLTKMNQDFFISPNEDGNKDFVAFKGLKNNVYNDLTVNVYAKDDH
QKQTPIWSSQAGASVSAIESTAWYGITARGSKVMPGDYQYVVTYRDEHGKEHQKQYTISVNDKKPMITQGRFDTINGVDHFTPDKTK
ALDSSGIVREEVFYLAKKNGRKFDVTEGKDGITVSDNKVYIPKNPDGSYTISKRDGVTLSDYYYLVEDRAGNVSFATLRDLKAVGKDK
AVVNFGLDLPVPEDKQIVNFTYLVRDADGKPIENLEYYNNSGNSLILPYGKYTVELLTYDTNAAKLESDKIVSFTLSADNNFQQVTFKIT
MLATSQITAHFDHLLPEGSRVSLKTAQDQLIPLEQSLYVPKAYGKTVQEGTYEVVVSLPKGYRIEGNTKVNTLPNEVHELSLRLVKVGD
ASDSTGDHKVMSKNNSQALTASATPTKSTTSATAKALPSTGEKMGLKLRIVGLVLLGLTCVFSRKKSTKD

SPy0430
Seq ID 170
MKWSGFMKTKSKRFLNLATLCLALLGTTLLMAHPVQAEVISKRDYMTRFGLGDLEDDSANYPSNLEARYKGYLEGYEKGLKGDDIPE
RPKIQVPEDVQPSDHGDYRDGYEEGFGEGQHKRDPLETEAEDDSQGGRQEGRQGHQEGADSSDLNVEESDGLSVIDEVVGVIYQA
FSTIWTYLSGLF

SPy0433
Seq ID 171
MKKTLTLLLALFAIGVTSSVRAEDEQSSTQKPVKFDLDGPQQKIKDYSGNTITLEDLYVGSKVVKIYIPQGWWVYLYRQCDHNSKERGI
LASPILEKNITKTDPYRQYYTGVPYILNLGEDPLKKGEKLTFSFKGEDGFYVGSYIYRDSDTIKKEKEAEEALQKKEEEKQQKQLEESM
LKQIREEDHKPWHQRLSESIQDQWWNFKGLFQ

SPy0437
Seq ID 172
MKKTLTLLLALFAIGVTSSVRAEDEQNKFILDGLQEKVKEVSVSDFSVGESKIKVWLPQAWSVKISREHSPKSSISNSGEQKPLSNSSE
NKEGQFSKRLPYGTQHTIKLSSQLTKGERVTLTFRDEDFWGAGYCFYRDSLSIKEDKQYEEEIKKIEDDLERQDLENDALEMFKKQTE
REANKPWHQRLSENIQDQWWNFKGLFQ

SPy0469
Seq ID 173
MIITKKSLFVTSVALSLVPLATAQAQEWTPRSVTEIKSELVLVDNVFTYTVKYGDTLSTIAEAMGIDVHVLGDINHIANIDLIFPDTILTANY
NQHGQATNLTVQAPASSPASVSHVPSSEPLPQASATSQPTVPMAPPATPSDVPTTPFASAKPDSSVTASSELTSSTNDVSTELSSES
QKQPEVPQEAVPTPKAAETTEVEPKTDISEAPTSANRPVPNESASEEVSSAAPAQAPAEKEETSAPAAQKAVADTTSVATSNGLSYA
PNHAYNPMNAGLQPQTAAFKEEVASAFGITSFSGYRPGDPGDHGKGLAIDFMVPENSALGDQVAQYAIDHMAERGISYVIWKQRFY
APFASIYGPAYTWNPMPDRGSITENHYDHVHVSFNA

SPy0488
Seq ID 174
LRQIQSIRLIDVLELAFGVGYKEETTSQFSSDQPSQVVLYRGEANTVRFAYTNQMSLMKDIRIALDGSDKSLTAQIVPGMGHVYEGFQT
SARGIFTMSGVPESTVPVANPNVQTKYIRYFKVIDDMHNTMYKGTVFLVQPQAWKYTMKSVDQLPVDDLNHIGVAGIERMTTLIKNAG
ALLTTGGSGAFPDNIKVSINPKGRQATITYGDGSTDIIPPAVLWKKGSVKEPTEADQSVGTPTPGIPGKFKRDQSLNEHEAMVNVEPLS
HVVKDNIKVIDEKSTGRFEPFRPNEDEKEKPASDVKVRPAEVGSWLEPATALPSVEMSAEDRLKS

SPy0515
Seq ID 175
MKVLLYLEAENYLRKSGIGRAIKHQAKALSLVGQHFTTNPRETYDLVHLNTYGLKSWLLMIKAQKAGKKVIMHGHSTEEDFRNSFIFSN
LLSPWFKKYLCHFYNKADAIITPTLYSKSLIESYGVKSPIFAVSNGIDLEQYGADPKKEAAFRRYFDIKEGEKVVMGAGLFFLRKGIDDF
VKVAQAMPDVRFIWFGETNKWVIPAQVRQMVNGNHPKNLIFPGYIKGDVYEGAMTGADAFFFPSREETEGIVVLEALASRQHLVLRDI
PVYYGWVDQSSAELATDIPGFIEALKKVFSGASNKVEAGYKVAQSRRLETVGHALVDVYKKVMEL

SPy0580
Seq ID 176
MENNNNHNIAEALSVSLHQIEQVLALTAQGNTIPFIARYRKEVTGNLDEVVIKSIIDMDKSLTTLNERKATILAKIEEQGKLTDQLRTSIEA
TEKLADLEELYLPYKEKRRTKATIAREAGLFPLARLILQNAQNLETAAEPFVTEGFASPQEALAGAVDILVEAMSEDAKLRSWTYNEIW
QYSRLVSTLKDEQLDEKKVFQIYYDFSDQVSNMQGYRTLALNRGEKLGILKVSFEHNLEKMQRFFSVRFKETNPYIEEVINQTIKKKIV
PAMERRVRSELSDAAEDGAIHLFSENLRHLLLVSPLKGKMVLGFDPAFRTGAKLAIVDQTGKLLTTQVIYPVAPASQTKIQAAKETLTQ
LIETYQIDIIAIGNGTASRESEAFVADVLKDFPNTSYVIVNESGASVYSASELARHEFPDLTVEKRSAISIARRLQDPLAELVKIDPKSIGV
GQYQHDVSQKKLSENLGFVVDTVVNQVGVNVNTASPSLLAHVSGLNKTISENIVKYREENGALTSRADIKKVPRLGAKAFEQAAGFLR

IPGAKNILDNTGVHPESYPAVKELFKVLGIQDLDDAAKATLAAVQVPQMAETLAIGQETLKDIIADLLKPGRDLRDDFEAPILRQDILDLK
DLEIGQKLEGTVRNVVDFGAFVDIGVHEDGLIHISEMSKTFVNHPSQVVSVGDLVTVWVSKIDLDRHKVNLSLLPPRDTH

SPy0621
Seq ID 177
MNEKVFRDPVHNYIHIDNPLIYDLINTKEFQRLRRIKQVPTTAFTFHGAEHSRFSHCLGVYEIARRVTAIFEEKYADIWNKDESLVTMTA
ALLHDIGHGAYSHTFEVLFHTDHEAFTQEIITNPETEINAILVRHAPDFPDKVASVINHTYPNKQVVQLISSQIDCDRMDYLLRDSYFSAA
NYGQFDLMRILRVIRPVEDGIVFEHSGMHAVEDYIVSRFQMYMQVYFHPASRAVELILQNLLKRAQHLYPEQQAYFQKTAPGLIPFFE
KKANLADYIALDDGVMNTYFQVWMASEDHILSDLASRFINRKILKSVTFDQDSQGELERLRQLVESVGFDPDYYTGIHINFDLPYDIYR
PELENPRTQIEMMQKDGSLAELSQLSPIVKALTGTTYGDRRFYFPKEMLELDDLFAPSKETFMSYISNGHFHFSQ

SPy0630
Seq ID 178
MDINLLQALLIGLWTAFCFSGMLLGIYTNRCIILSFGVGIILGDLPTALSMGAISELAYMGFGVGAGGTVPPNPIGPGIFGTLMAITSAGKV
TPEAALALSTPIAVAIQFLQTFAYTAFAGAPETAKKQLQKGNIRGFKFAANGTIWAFAFIGLGLGLLGALSMDTLLHLVDYIPPVLLNGLT
VAGKMLPAIGFAMILSVMAKKELIPFVLIGYVCAAYLQIPTIGIAIIGIIFALNEFYNKPKQVDATTVQGGQQDDWI

SPy0681
Seq ID 179
LTPRSGKTTAGHFRYARYLIESEDENHLVTAYNQEQAYRLFIDGDGTGLMHIFDGNCEIKHDERGDHLLITTPKGNKRVYYKGGGKVN
SVGAITGMSLGSVVFCEINLLHMDFIQECFRRTWAAKLRYHLADLNPPAPQHPVIKDVFDVQNTRWTHWTMDDNPILTAERKQNIINS
LKKNPYLYKRDVLGQRVMPQGVIYGLFDTEKNVLDALIGEPVEMYFCADGGQSDATSMSCNIVTRVRDNGRISFRLNRVAHYYHSGA
DTGQVKAMSTYALELKVFIDWCVKKYQMRYTEVFVDPACKSLREELHKLGVFTLGAPNNSKDVSSKAKGIEVGIERGQNIISDGAFYL
VNHSEEEYDHYHFLKEIGLYSRDDNGKPIDKDNHAMDEFRYSVNVFVHRYYN

SPy0683
Seq ID 180
MKKKPIKLNDEQLLLEASQLSDMYHQLTLDLFDQVIERIKARGSASLADNPYLWQANKLHDVGLLNADNIKLIAKYSGIAEAQLRYIIKNE
GFKIYKNTSEQLEEALGRESGVNSTIQDDLSNYARQAIDDVHNLTNTTLPFSVIGAYQGIIQDAVAGVVTGLKTPDQAINQTVIKWFKKG
FYGFTDKAGRKWRADSYARTVINTTTWRVFNEAKEAPAREFGIDTFYYSKKATAREMCAPLQHQIVTTGEAREEGGIKILALSDYGHG
EPDGCLGINCKHTKTPFVVGVNSKPELPEHLKNITPAQAKANANAQAKQRAIERSIRKSKELLHVAKQLGDKELIRQYQSDVRSKQDA
LNYLINNNAFLHRNQAREKRYNNPYTKTQSEVEVRKEKAKLDKRRDVESAIIGVETSEGIPLKITKHLAERAVLRNIAPIDIVDSIKEPLKI
APIKYDNLDRPSQKYIGKCVSTVINPIDGNIVTVHATSTRIRKKYGGN

SPy0702
Seq ID 181
MSRDPTLILDESNLVIGKDGRVHYTFTTEDDNPKVRLASKCLGTAHFNQLMIERGDQATSYVAPVVVEGTGNPTGLFKDLKEISLELTD
TANSQLWSKIKLTNRGMLQEYYDGKIKTEIVNSARGVATRISEDTDKKLALINDTIDGIRREYRDADRKLSASYQAGIEGLKATMANDKI
GLQAEIKASAQGLSQKYDDELRKLSAKITTTSSGTTEAYESKLAGLRAEFTRSNQGTRTELESQISGLRAVQQSTASQISQEIRDREGA
VSRVQQSLESYQRRMQDAEENYSSLTHTVRGLQSDVGSPTGKIQSRLTQLAGQIEQRVTRDGVMSIISGAGDSIKLAIQKAGGINAKM
SGNEIISAINLNSYGVTIAGKHIALDGNTTVNGTFTTKIAEAIKIRADQIIAGTIDAARIRVINLNASSIVGLDANFIKAKIGYAITDLLEGKVIK
ARNGAMLIDLNTAKMDFNSDATINFNSKNNALVRKDGTHTAFVHFSNATPKGYTGSALYASIGITSSGDGVNSASSGRFAGLRSFRYA
TGYNHTAAVDQTEIYGDNVLVVDDFNITRGFKFRPDKMQKMLDMNDLYAAVVALGRCWGHLANVGWNTAHSNFTSAVNRELNNYIT
KI

SPy0710
Seq ID 182
MTFLDKIKQGCLDGWAKYKILPSLTAAQAILESGWGKHAPHNALFGIKADSSWTGKSFDTKTQEEYQAGVVTDIVDRFRAYDSWDESI
ADHGQFLVDNPRYEAVIGETDYKKACYAIKAAGYATASSYVELLIQLIEENDLQSWDREALKNNKEETMTTANEIVQYCVNLANSGMG
VDKDGAHGTQCCDLPCFVAKNWFGVDLWGNAIDLLDSASAQGWEVHRMPTEANPKAGATFVQSVPYHQFGHTGIVIEDSDGYTMR
TVEQNIDGNPDALYVGAPARFNTRDFTGVIGWFYPPYQGDTVTQPVSTEPQTSDTIVETAKTGTFTLDVAEINIRRWPSLASEVVGIYK
QGDTVSFDSEGYANGYYWISYVGGSGMRNYLGIGQTDKDGNRISLWGKLN

SPy0711
Seq ID 183
MKKINIIKIVFIITVILISTISPIIKSDSKKDISNVKSDLLYAYTITPYDYKNCRVNFSTTHTLNIDTQKYRGKDYYISSEMSYEASQKFKRDDH
VDVFGLFYILNSHTGEYIYGGITPAQNNKVNHKLLGNLFISGESQQNLNNKIILEKDIVTFQEIDFKIRKYLMDNYKIYDATSPYVSGRIEIG
TKDGKHEQIDLFDSPNEGTRSDIFAKYKDNRIINMKNFSHFDIYLEK

SPy0720
Seq ID 184
MITTFETILDKIKAHQTIIIHRHQNPDPDALGSQAGLKEIIAQNFPDKKVLMTGFDEPSLAWISQMDQVTDKDYKEALVIITDTANRPRIDD
ERYTLGKCLIKIDHHPNDDVYGDFYYVDTSASSASEIIADFAFSQNLTLSDKAAKLLYTGIVGDTGRFLYASTTSKTLSIASQLRHFEFDF
AAISRQMDSFPLKIAKLQSYVFEHLTIDESGAAYVLVSQETLKHFDVTLAESSAIVCAPGKIDNVQAWAIFVELTDGNYRVRMRSKEKII
NGIAKRHGGGGHPLASGANSANLEENQAIFRELIAVCQEI

SPy0727
Seq ID 185
MIEENKHFEKKMQEYDASQIQVLEGLEAVRMRPGMYIGSTAKEGLHHLVWEIVDNSIDEALAGFASHIKVFIEADNSITVVDDGRGIPV
DIQAKTGRPAVETVFTVLHAGGKFGGGGYKVSGGLHGVGSSVVNALSTQLDVRVYKNGQIHYQEFKRGAVVADLEVIGTTDVTGTTV
HFTPDPEIFTETTQFDYSVLAKRIQELAFLNRGLKISITDKRSGMEQEEHFLYEGGIGSYVEFLNDKKDVIFETPIYTDGELEGIAVEVAM
QYTTSYQETVMSFANNIHTHEGGTHEQGFRAALTRVINDYAKKNKILKENEDNLTGEDVREGLTAVISVKHPNPQFEGQTKTKLGNSE
VVKITNRLFSEAFQRFLLENPQVARKIVEKGILASKARIAAKRAREVTRKKSGLEISNLPGKLADCSSNDANQNELFIVEGDSAGGSAKS
GRNREFQAILPIRGKILNVEKATMDKILANEEIRSLFTAMGTGFGADFDVSKARYQKLVIMTDADVDGAHIRTLLLTLIYRFMRPVLEAG
YVYIAQPPIYGVKVGSEIKEYIQPGIDQEDQLKTALEKYSIGRSKPTVQRYKGLGEMDDHQLWETTMDPENRLMARVTVDDAAEADKV
FDMLMGDRVEPRRDFIEENAVYSTLDI

SPy0737
Seq ID 186
MRKVKKVFVSSCMLLTVGLGVAVPTGFSQSNGVMVVKAAEVPATDLSRQASDSERVDESSLLQKENLSVDSFKLENLNGWEAENDT
AGNLGKFKDPDSSGYQNILTSSGKNISVAVAPKGSGKMNIKVTKRSNFQGGYYVGGLRTQTPVLKLNDVYRYSFTTKKLSGNSSEFK
TRVKPVESNNKLGKELVIRVDNKNVSTKHDWLPDISDGTHTVDFTGLDKKLSVAFRFSPRQTSNVVYEFSNINIKNISPASVPAIPSKVL
EGTSVLSGTAISSGDTLEKRKSFDGDILRVYKDSKIIARTVIKGNKWDVKLSKPLIAGEKLDFEILHPRSQNVSKKISKQVEAKPFDPASY
KEKVIAKLKPVYEATSEKITNDAWLDENAKDLQKQKLEEQYISGKVAISEAGTKQEAIDAAYNKYSSQTDPDSLPSQYKQGNKENEQE
KGRQDLIQTRDLTLKAIQEDKWLTEQEKTIQKEEALKAFETGIESVNQTVSLEQLKQRLIVYKASEKDSEKKEYPESIPNQHIPGKEKEV
KAAKQEELKKLHDTTLEKINQDKWLTPDQQAEQLKQAEVTFKKGQEAIKSAQTLTQLETDLADYVSENEGKGNSIPDKYKSGNKDDL
VNKAEVKLKEAHEATKQAIEKDPWLSPEQKKAQKEKAKARLDEGLKALKAADSLEILKVTEEAFVDKEKNPDSIPNQHKAGTADQARK
QALDSLDKEVQKELESIDNDNTLTTDEKAAAKKKVNDAYDVAKQTAMEANSYEDLTTIKDEFLSNLPHKQGTPLKDQQSDAIAELEKK
QQEIEKAIEGDKTLPRDEKEKQIADSKERLKSDTQKVKDAKNADAIKKAFEEGKVNIPQAHIPGDLNKDKEKLLAELKQKADDTEKAIDV
DKTLTEDEKKEQKVKTKAELEKAKTDVKNTQTREELDKKVPELKKAIEDTHVKGNLEGVKNKAIEDLKKAHTETVAKINGDDTLDKATK
EAQVKEADKALAAGKDAITKADDADKVSTAVTEHTPKIKAAHKTGDLKKAQVDANTALDKAAEKERGEINKDATLTTEDKAKQLKEVE
TALTKAKDNVKAAKTADAINDARDKGVATIDAVHKAGQDLGARKSGQVAKLEEAAKATKDKISADPTLTSKEKEEQSKAVDAELKKAIE
AVNAADTADKVDDALGEGVTDIKNQHKSGDSIDARREAHGKELDRVAQETKGAIEKDPTLTTEEKAKQVKDVDAAKERGMAKLNEAK
DADALDKAYGEGVTDIKNQHKSGDPVDARRGLHNKSIDEVAQATKDAITADTTLTEAEKETQRGNVDKEATKAKEELAKAKDADALD
KAYGDGVTSIKNQHKSGKGLDVRKDEHKKALEAVAKRVTAEIEADPTLTPEVREQQKAEVQKELELATDKIAEAKDADEADKAYGDG
VTAIENAHVIGKGIEARKDLAKKDLAEAAAKTKALIIEDKTLTDDQRKEQLLGVDTEYAKGIENIDAAKDAAGVDKAYSDGVRDILAQYKE
GQNLNDRRNAAKEFLLKEADKVTKLINDDPTLTHDQKVDQINKVEQAKLDAIKSVDDAQTADAINDALGKGIENINNQYQHGDGVDVR
KATAKGDLEKEAAKVKALIAKDPTLTQADKDKQTAAVDAAKNTAIAAVDKATTTEGINQELGKGITAINKAYRPGEGVKARKEAAKADL
EKEAAKVKALITNDPTLTKADKAKQTEAVAKALKAAIAAVDKATTAEGINQELGKGITAINKAYRPGEGVKARKEAAKADLEREAAKVR
EAIANDPTLTKADKAKQTEAVAKALKAAIAAVDKATTAEGINQELGKGITAINKAYRPGEGVEAHKEAAKANLEKVAKETKALISGDRYL
SETEKAVQKQAVEQALAKALGQVEAAKTVEAVKLAENLGTVAIRSAYVAGLAKDTDQATAALNEAKQAAIEALKQAAAETLAKITTDAK
LTEAQKAEQSENVSLALKTAIATVRSAQSIASVKEAKDKGITAIRAAYVPNKAVAKSSSANHLPKSGDANSIVLVGLGVMSLLLGMVLYS
KKKESKD

SPy0747
Seq ID 187
MINKKCIIPVSLLTLAITLTSVEEVTSRQNLTYANEIVTQRPKRESVISDKSNFPVISPYLASVDFGERKTPLPTPDKGVKVTTEQSIAQVR
KGPEERPYTVTGKITSVINGWGGYGFYIQDSEGIGLYVYPQKDLGYSKGDIVQLTGTLTRFKGDLQLQQVTAHKKLELSFPTSVKEAVI
SELETTTPSTLVKLSHVTVGELSTDQYNNTSFLVRDDSGKSIVVHIDHRTGVKGADVVTKISQGDLINLTAILSIVDGQLQLRPFSLEQLE
VVKKVTSSNSDASSRNIVKIGEIQGASHTSPLLKKAVTVEQVVVTYLDDSTHFYVQDLNGDGDLATSDGIRVFAKNAKVQVGDVLTISG
EVEEFFGRGYEERKQTDLTITQIVAKAVTKTGTAQVPSPLVLGKDRIAPANIIDNDGLRVFDPEEDAIDYWESMEGMLVAVDDAKILGP
MKNKEIYVLPGSSTRPLNNSGGVLLPANSYNTDVIPVLFKKGKQIIKAGDSYKGRLAGPVSYSYGNYKVFVDDSKNMPSLMDGHLKPE
KTNLQKDLSKLSIASYNIENFSANPSSTKDEKVKRIAESFIHDLNAPDIIGLIEVQDNNGPTDDGTTDATQSAQRLIDAIKKLGGPTYRYV
DIAPENNVDGGQPGGNIRTGFLYQPERVSLSDKPKGGARDALTWVNGELNLSVGRIDPTNAAWKDVRKSLAAEFIFQGRKVVVVAN
HLNSKRGDNALYGCVQPVTFKSEQRRHVLANMLAQFAKEGAKHQANIVMLGDFNDFEFTKTIQLIEEGDMVNLVSRHDISDRYSYFH
QGNNQTLDNILVSRHLLDHYEFDMVHVNSPFMEAHGRASDHDPLLLQLSFSKENDKAESSKQSVKAKKTSKGKLLPKTGDSLVYVITL
LGTASLLVPILLLTKGKKES

SPy0777
Seq ID 188
VISFAPFLSPEAIKHLQENERCRDQSQKRTAQQIEAIYTSGQNILVSASAGSGKTFVMVERILDKILRGVSIDRLFISTFTVKAATELRERI
ENKLYSQIAQTTDFQMKVYLTEQLQSLCQADIGTMDAFAQKVVSRYGYSIGISSQFRIMQDKAEQDVLKQEVFSKLFNEFMNQKEAPV
FRALVKNFSGNCKDTSAFRELVYTCYSFSQSTENPKIWLQENFLSAAKTYQRLEDIPDHDIELLLLAMQDTANQLRDVTDMEDYGQLT
KAGSRSAKYTKHLTIIEKLSDWVRDFKCLYGKAGLDRLIRDVTGLIPSGNDVTVSKVKYPVFKTLHQKLKQFRHLETILMYQKDCFSLLE
QLQDFVLAFSEAYLAVKIQESAFEFSDIAHFAIKILEENTDIRQSYQQHYHEVMVDEYQDNNHMQERLLTLLSNGHNRFMVGDIKQSIY
RFRQADPQIFNQKFRDYQKKPEQGKVILLKENFRSQSEVLNVSNAVFSHLMDESVGDVLYDEQHQLIAGSHAQTVPYLDRRAQLLLY
NSDKDDGNAPSDSEGISFSEVTIVAKEIIKLHNDKGVPFEDITLLVSSRTRNDIISHTFNQYGIPIATDGGQQNYLKSVEVMVMLDTLRTI
NNPRNDYALVALLRSPMFAFDEDDLARIALQKDNELDKDCLYDKIQRAVIGRGAHPELIHDTLLGKLNVFLKTLKSWRRYAKLGSLYDL
IWKIFNDRFYFDFVASQAKAEQAQANLYALALRANQFEKSGYKGLYRFIKMIDKVLETQNDLADVEVATPKQAVNLMTIHKSKGLQFPY
VFILNCDKRFSMTDIHKSFILNRQHGIGIKYLADIKGLLGETTLNSVKVSMETLPYQLNKQELRLATLSEEMRLLYVAMTRAEKKVYFIGK
ASKSKSQEITDPKKLGKLLPLALREQLLTFQDWLLAIADIFSTEDLYFDVRFIEDSDLTQESVGRLQTPQLLNPDDLKDNRQSETIARAL
DMLEAVSQLNANYEAAIHLPTVRTPSQLKATYEPLLEPIGVDIIEKSSRSLSDFTLPHFSKKAKVEASHIGSALHQLMQVLPLSKPINQQ
TLLDALRGIDSNEEVKTALDLKKIESFFCDTSLGQFFQTYQKHLYREAPFAILKLDPISQEEYVLRGIIDAYFLFDDHIVLVDYKTDKYKQP
IELKKRYQQQLELYAEALTQTYKLPVTKRYLVLMGGGKPEIVEV

SPy0789
Seq ID 189
MVKTDFKLRYQGSAIGYLWSILKPLMMFTIMYLVFIRFLRLGGNVPHFPVALLLANVIWSFFSEATSMGMVSIVSRGDLLRKLNFSKHII
VFSAVLGALINFLINLVVVLIFALINGVTISGYAYLSLFLFIELVVLVLGIALLLSNVFVYYRDLAQVWEVLLQAGMYATPIIYPITFVLDSHPL
AAKLLMLNPVAQMIQDFRYLLIDRANVTIWQMSTNWFYIVIPYLVPFVILFIGIFVFKKNADRFAEII

SPy0839
Seq ID 190
MTFLSDLISLMTKIRLSWVIKAGIFQLLFVTIANIVLSEFFYFILDVTGQYHLDKDNVVTFLKNPIALALLGAYLFLLAAFIHLEFFALYRIIAD
QEISFYLFRKQFSYYLRGLWKTFSGYQLLLFLLYILLTIPVLHIGLSSVITQKLYLPEFIVGELSKITSTKYLLYGSLILVFYLNLRLVYFLPLI
AINHRTVAQAWRESWQKTKKKHVLLWMKLFAINGLTIVVLSLAISMILIFVDMFNPKGNNIIVQLGALTFTWELIFFTTIFFKLCSAMILKE
AIEPQKQYDEPRRSNKAYVVIFIVVTVGFAYQSLERLTFFDTSHSKTVIAHRGLVSAGVENSLEALEGAKKAGSDYVELDLILTKDNHFV
VSHDNRLKRLAGVNKTIRNLTLKEVEHLTSHQGHFSGRFVSFDTFYQKAKKLNMPLLIELKPIGTEPGNYVDLFLETYHRLGISKDNKV
MSLDLEVIEAIKKKNPSITTGYIIPIQFGFFGDEFVDFYVIEDFSYRSYLSSQAFWNNKEIYVWTINDPKRIEHYLLKPIQGIITDQPALTNQ
LIKDLKQDNSYFSRLVRIISSLY

SPy0843

Seq ID 191
MKKHLKTVALTLTTVSVVTHNQEVFSLVKEPILKQTQASSSISGADYAESSGKSKLKINETSGPVDDTVTDLFSDKRTTPEKIKDNLAKG
PREQELKAVTENTESEKQITSGSQLEQSKESLSLNKTVPSTSNWEICDFITKGNTLVGLSKSGVEKLSQTDHLVLPSQAADGTQLIQVA
SFAFTPDKKTAIAEYTSRAGENGEISQLDVDGKEIINEGEVFNSYLLKKVTIPTGYKHIGQDAFVDNKNIAEVNLPESLETISDYAFAHLA
LKQIDLPDNLKAIGELAFFDNQITGKLSLPRQLMRLAERAFKSNHIKTIEFRGNSLKVIGEASFQDNDLSQLMLPDGLEKIESEAFTGNP
GDDHYNNRVVLWTKSGKNPSGLATENTYVNPDKSLWQESPEIDYTKWLEEDFTYQKNSVTGFSNKGLQKVKRNKNLEIPKQHNGVT
ITEIGDNAFRNVDFQNKTLRKYDLEEVKLPSTIRKIGAFAFQSNNLKSFEASDDLEEIKEGAFMNNRIETLELKDKLVTIGDAAFHINHIYA
IVLPESVQEIGRSAFRQNGANNLIFMGSKVKTLGEMAFLSNRLEHLDLSEQKQLTEIPVQAFSDNALKEVLLPASLKTIREEAFKKNHLK
QLEVASALSHIAFNALDDNDGDEQFDNKVVVKTHHNSYALADGEHFIVDPDKLSSTIVDLEKILKLIEGLDYSTLRQTTQTQFRDMTTA
GKALLSKSNLRQGEKQKFLQEAQFFLGRVDLDKAIAKAEKALVTKKATKNGQLLERSINKAVLAYNNSAIKKANVKRLEKELDLLTGLV
EGKGPLAQATMVQGVYLLKTPLPLPEYYIGLNVYFDKSGKLIYALDMSDTIGEGQKDAYGNPILNVDEDNEGYHALAVATLADYEGLDI
KTILNSKLSQLTSIRQVPTAAYHRAGIFQAIQNAAAEAEQLLPKPGTHSEKSSSSESANSKDRGLQSNPKTNRGRHSAILPRTGSKGSF
VYGILGYTSVALLSLITAIKKKKY

SPy0872
Seq ID 192
MKKYFILKSSVLSILTSFTLLVTDVQADQVDVQFLGVNDFHGALDNTGTAYTPSGKIPNAGTAAQLGAYMDDAEIDFKQANQDGTSIRV
QAGDMVGASPANSALLQDEPTVKVFNKMKFEYGTLGNHEFDEGLDEFNRIMTGQAPDPESTINDITKQYEHEASHQTIVIANVIDKKT
KDIPYGWKPYAIKDIAINDKIVKIGFIGVVTTEIPNLVLKQNYEHYQFLDVAETIAKYAKELQEQHVHAIVVLAHVPATSKDGVVDHEMAT
VMEKVNQIYPEHSIDIIFAGHNHQYTNGTIGKTRIVQALSQGKAYADVRGTLDTDTNDFIKTPSANVVAVAPGIKTENSDIKAIINHANDIV
KTVTERKIGTATNSSTISKTENIDKESPVGNLATTAQLTIAKKTFPTVDFAMTNNGGIRSDLVVKNDRTITWGAAQAVQPFGNILQVIQM
TGQHIYDVLNQQYDENQTYFLQMSGLTYTYTDNDPKNSDTPFKIVKVYKDNGEEINLTTTYTVVVNDFLYGGGDGFSAFKKAKLIGAIN
TDTEAFITYITNLEASGKTVNATIKGVKNYVTSNLESSTKVNSAGKHSIISKVFRNRDGNTVSSEVISDLLTSTENTNNSLGKKETTTNKN
TISSSTLPITGDNYKMSPIMTILALISLGGLNAFIKKRKS

SPy0895
Seq ID 193
MTNNQTLDILLDVYAYNHAFRIAKALPNIPKTALYLLEMLKERRELNLAFLAEHAAENRTIEDQYHCSLWLNQSLEDEQIANYILDLEVKV
KNGAIIDFVRSVSPILYRLFLRLITSEIPNFKAYIFDTKNDQYDTWHFQAMLESDHEVFKAYLSQKQSRNVTTKSLADMLTLTSLPQEIKD
LVFLLRHFEKAVRNPLAHLIKPFDEEELHRTTHFSSQAFLENIITLATFSGVIYRREPFYFDDMNAIIKKELSLWRQSIV

SPy0972
Seq ID 194
MKTTSLIKVDLPSTIGIGYGAFWRSRNFYRVVKGSRGSKKSKTTALNFIVRLLKYPWANLLVIRRYSNTNKQSTYTDFKWACNQLKVT
HLFKFNESLPEITVKATGQKILFRGLDDELKITSITVDVGALCWAWFEEAYQIETEDKFSTVVESIRGSLDAPDFFKQITVTFNPWSERH
WLKRVFFDEETKRADTFSGTTTFRVNEWLDDVDKRRYEDLYKTNPRRARIVCDGEWGVAEGLVFDNFEVVDFDVEKTIQRVKETSA
GMDFGFTQDPTTLICVAVDLANKELWLYNEHYQKAMLTDHIVKMIRDKNLHRSYIAGDSAEKRLIAEIKSKGVSGIVPSIKGKGSIMQGI
QFMQGFKIYIHPSCEHTIEEFNTYTFKQDKEGNWLNEPIDKNNHVIDAIRYALEKYHIRSNESNQFEVLRAGFGY

SPy0981
Seq ID 195
MAEETQTVETVEEQVVPEAKQPQDEKKYTDADVDAIIDKKFAKWKSEQEAEKSEAKKMAKMNEKEKADYEKQKLLDELQELKNDKT
RNELTAVARQMFAESEINVNDDVLGLVVTLDAEQTKANVTTLANAFAKVIADDRKALVRQTTPSTGGGLSKQTNYGANLASKAAQQS
TKLF

SPy1008
Seq ID 196
MRYNCRYSHIDKKIYSMIICLSFLLYSNVVQANSYNTTNRHNLESLYKHDSNLIEADSIKNSPDIVTSHMLKYSVKDKNLSVFFEKDWIS
QEFKDKEVDIYALSAQEVCECPGKRYEAFGGITLTNSEKKEIKVPVNVWDKSKQQPPMFITVNKPKVTAQEVDIKVRKLLIKKYDIYNN
REQKYSKGTVTLDLNSGKDIVFDLYYFGNGDFNSMLKIYSNNERIDSTQFHVDVSIS

SPy1032
Seq ID 197
VNTYFCTHHKQLLLYSNLFLSFAMMGQGTAIYADTLTSNSEPNNTYFQTQTLTTTDSEKKVVQPQQKDYYTELLDQWNSIIAGNDAYD
KTNPDMVTFHNKAEKDAQNIIKSYQGPDHENRTYLWEHAKDYSASANITKTYRNIEKIAKQITNPESCYYQDSKAIAIVKDGMAFMYEH
AYNLDRENHQTTGKENKENWVVYEIGTPRAINNTLSLMYPYFTQEEILKYTAPIEKFVPDPTRFRVRAANFSPFEANSGNLIDMGRVK
LISGILRKDDLEISDTIKAIEKVFTLVDEGNGFYQDGSLIDHVVTNAQSPLYKKGIAYTGAYGNVLIDGLSQLIPIIQKTKSPIKADKMATIYH
WINHSFFPIIVRGEMMDMTRGRSISRFNAQSHVAGIEALRAILRIADMSEEPHRLALKTRIKTLVTQGNAFYNVYDNLKTYHDIKLMKEL
LSDTSVPVQKLDSYVASFNSMDKLALYNNKHDFAFGLSMFSNRTQNYEAMNNENLHGWFTSDGMFYLYNNDLGHYSENYWATVNP
YRLPGTTETEQKPLEGTPENIKTNYQQVGMTGLSDDAFVASKKLNNTSALAAMTFTNWNKSLTLNKGWFILGNKIIFVGSNIKNQSSH
KAYTTIEQRKENQKYPYCSYVNNQPVDLNNQLVDFTNTKSIFLESDDPAQNIGYYFFKPTTLSISKALQTGKWQNIKADDKSPEAIKEV
SNTFITIMQNHTQDGDRYAYMMLPNMTRQEFETYISKLDIDLLENNDKLAAVYDHDSQQMHVIHYGKKATMFSNHNLSHQGFYSFPH
PVRQNQQ

SPy1054
Seq ID 198
LLTFGGASAVKAEENEKVREQEKLIQQLSEKLVEINDLQTLNGDKESIQSLVDYLTRRGKLEEEWMEYLNSGIQRKLFVGPKGPAGEK
GEQGPTGKQGERGETGPAGPRGDKGETGDKGAQGPVGPAGKDGQNGKDGLPGKDGKDGQNGKDGLPGKDGKDGQDGKDGLP
GKDGKDGQNGKDGLPGKDGQPGKPAPKTPEVPQNPDTAPHTPKTPRIPGQSKDVTPAPQNPSNRGLNKPQTQGGNQLAKTPAAH
DTHRQLPATGETTNPFFTAAAVAIMTTAGVVAVAKRQENN

SPy1063
Seq ID 199
MYIFSSSKKDSAKELVILTPNSQTILTGTIPAFEEKYGVKVRLIQGGTGQLIDQLGRKDKPLNADIFFGGNYTQFESHKDLFESYVSPQV
STVISDYQLPSHRATPYTINGSVLIVNNELARGLHITSYEDLLQPALKGKIAFADPNSSSSAFSQLTNILLAKGGYTNADAWAYMKRLLV
NMNSIRATSSSEVYQSVAEGKMIVGLTYEDPCINLQKSGANVSIVYPKEGTVFVPSSVAIIKHAPNMTEAKLFINFMLSRDVQNAFGQS

TSNRPIRQDAQTSHDMKALETIATLKEDYAYVTKHKKKIVATYNQLRQRLEKAK

SPy1162
Seq ID 200
MPTSIKAIKESLEAVTSLLDPLFQELATDTRSGVQKALKSRQKVIQAELAEEERLEAMLSYEKALYKKGYKAIAGIDEVGRGPLAGPVVA
ACVILPKYCKIKGLNDSKKIPKAKHETIYQAVKEKALAIGIGIIDNQLIDEVNIYEATKLAMLEAIKQLEGQLTQPDYLLIDAMTLDIAISQQSI
LKGDANSLSIAAASIVAKVTRDQMMANYDRIFPGYDFAKNAGYGTKEHLQGLKAYGITPIHRKSFEPVKSMCCDSTNP

SPy1206
Seq ID 201
MTVKEETMSILEVKQLSHGFGDRAIFENVSFRLLKGEHIGLVGANGEGKSTFMSIVTGHLQPDEGKVEWSKYVTAGYLDQHTVLESG
QTVRDVLRTAFDELFKTENRINEIYASMADDKADIAVLMEEVGELQDRLESRDFYTLDAKIDEVARALGVMDFGMESDVTSLSGGQRT
KVLLAKLLLEKPDILLLDEPTNHLDAEHIEWLKRYLQHYENAFVLISHDISFLNDVINIVYHVENQSLVRYTGDYYQFQAVYEMKQSQLE
AAYERQQKEIANLQDFVNRNKARVATRNMAMSRQKKLDKMDIIELQAEKPKPNFEFKQARTPSRFIFQTKNLVIGYDYPLTKEPLNITF
ERNQKIAIVGANGIGKSTLLKSLLGVIEPLEGHIVTGDFLEVGYFEQEVTGVNRQTPLEVVWDAFPALNQAEVRAALARCGLTSKHIES
QIQVLSGGEQAKVRFCLLMNRENNVLILDEPTNHLDIDAKNELKRALKAYKGSILMVCHEPDFYNGWVTDTWDFSKLT

SPy1228
Seq ID 202
MNKKFIGLGLASVAVLSLAACGNRGASKGGASGKTDLKVAMVTDTGGVDDKSFNQSAWEGLQSWGKEMGLQKGTGFDYFQSTSE
SEYATNLDTAVSGGYQLIYGIGFALKDAIAKAAGDNEGVKFVIIDDIIEGKDNVASVTFADHEAAYLAGIAAAKTTKTKTVGFVGGMEGT
VITRFEKGFEAGVKSVDDTIQVKVDYAGSFGDAAKGKTIAAAQYAAGADVIYQAAGGTGAGVFNEAKAINEKRSEADKVWVIGVDRD
QKDEGKYTSKDGKEANFVLASSIKEVGKAVQLINKQVADKKFPGGKTTVYGLKDGGVEIATTNVSKEAVKAIKEAKAKIKSGDIKVPEK

SPy1245
Seq ID 203
MKMKKKFFLLSLLALSTFFLSACSSWIDKGESITAVGSTALQPLVEAVADEFGSSNLGKTVNVQGGGSGTGLSQVQSGAVQIGNSDV
FAEEKDGIDASKLVDHQVAVAGLAVIANPKVKVSNLSSQQLQKIFSGEYTNWKQVGGEDLAISVINRAASSGSRATFDSVIMKGVNAK
QSQEQDSNGMVKSIVSQTPGAISYLSFAYVDSSVKSLQLNGFKANAKNVATNDWPIWSYEHMYTKDKPTGLTKEFLDYMFSDEVQQ
NIVTHMGYISINDMEVVKSHDGKVTKR

SPy1315
Seq ID 204
MTHKIKVLLLAIMSIFLTCNIASAETIAIVSDTAYAPFEFKDSDQIYKGIDVDIINEVAKRQSWDFSMSFPGFDAAVNAVQSGQASALMAG
TTITNARKKVFHFSEPYYDTKIVIATRKANAIKKYSDLKGKTVGVKNGTAAQAFLNNYKKKYDYTVKTFDTGDLMYNSLSAGSIAAVMD
DEAVIQYAISQNQDIAINMKGEPIGSFGFAVKKGSGYDYLVNDFNTALKAMKADGTYQAIMTKWLGTDDKATTSQATGNPSAKATPTK
DSYKIVSDSSFAPFEFQNGKGKYVGIDIELIKAIAKQQGFKIEIANPGFDAALNAVQSSQADGVIAGATITDARKAIFDFSDPYYTSNIILA
VKAGKNIKNYEDLDRKTVGAKNGTSSYSWLKENAPKYGYNVKAFDDGSSMYDSLNSGSVDAIMDDEAVLKYAISQGRRFETPLEGIS
TGEVGFAVKKGTNPELIEMFNNGLAALKKSGQYDDIIDKYLDSKKAATPSEKGADESTISGLLSNNYKQLLAGLGTTLSLTLISFAIAIIGI
IFGMMAVSPTKSLRLISTVFVDVVRGIPLMIVAAFIFWGVPNLIESMTGHQSPINDFLAATIALSLNGGAYIAEIVRGGIEAVPAGQMEAS
RSLGLSYGTTMRKVILPQAVKLMLPNFINQFVISLKDTTIVSAIGLVELFQTGKIIIARNYQSFRMYAILAIIYLIMIILLTRLAKRLEKRLN

SPy1357
Seq ID 205
MGKEIKVKCFLRRSAFGLVAVSASVLVGSTVSAVDSPIEQPRIIPNGGTLTNLLGNAPEKLALRNEERAIDELKKQAIEDKEATTAIEAAS
SDALEALADQTDALQSEEAAVVKADNAASDALEALADQTDALQSEEAEVVQSDNAASDAWEKAATPIALDVKKTKDTKPVVKKEERQ
NVNTLPTTGEESNPFFTAAALAIMVSTGVLVVSSKCKEN

SPy1361
Seq ID 206
MKTKKVIILVGLLLSSQLTLIACQSRGNGTYPIKTKQSRKGMTSNKIKPIKKSKKTNKTHKGVAGVDFPTDDGFILTKDSKILSKTDQGIV
VDHDGHSHFIFYADLKGSPFEYLIPKGASLAKPAVAQRAASQGTSKVADPHHHYEFNPADIVAEDALGYTVRHDDHFHYILKSSLSGQ
TQAQAKQVATRLPQTSSLVSTATANGIPGLHFPTSDGFQFNGQGIVGVTKDSILVDHDGHLHPISFADLRQGGWAHVADQYDPAKKA
EKPAETHQTPELSEREKEYQEKLAYLAEKLGIDPSTIKRVETQDGKLGLEYPHHDHAHVLMLSDIEIGKDIPDPHAIEHARELEKHKVG
MDTLRALGFDEEVILDIVRTHDAPTPFPSNEKDPNMMKEWLATVKIKLDLGSRKDPLQRKGLSLLPNLETLGIGFTPIKDISPVLQFKKLK
QLLMTKTGVTDYRFLDNMPQLEGIDISQNNLKDISFLSKYKNLTLVAAADNGIEDIRPLGQLPNLKFLVLSNNKISDLSPLASLHQLQELH
IDNNQITDLSPVSHKESLTVVDLSRNADVDLATLQAPKLETLMVNDTKVSHLDFLKNNPNLSSLSINRAQLQSLEGIEASSVIVRVEAEG
NQIKSLVLKDKQGSLTFLDVTGNQLTSLEGVNNFTALDILSVSKNQLTNVNLSKPNKTVTNIDISHNNISLADLKLNEQHIPEAIAKNFPA
VYEGSMVGNGTAEEKAAMATKAKESAQEASESHDYNHNHTYEDEEGHAHEHRDKDDHDHEHEDENEAKDEQNHAD

SPy1371
Seq ID 207
LAKQYKNLVNGEWKLSENEITIYAPATGEELGSVPAMTQAEVDAVYASAKKALSDWRALSYVERAAYLHKAADILVRDAEKIGAILSKE
VAKGHKAAVSEVIRTAEIINYAAEEGLRMEGEVLEGGSFEAASKKKIAIVRREPVGLVLAISPFNYPVNLAGSKIAPALIAGNVVALKPPT
QGSISGLLLAEAFAEAGIPAGVFNTITGRGSVIGDYIVEHEAVSFINFTGSTPIGEGIGKLAGMRPIMLELGGKDSAIVLEDADLALAAKNI
VAGAFGYSGQRCTAVKRVLVMDKVADQLAAEIKTLVEKLSVGMPEDDADITPLIDTSAADFVEGLIKDATDKGATALTAFNREGNLISP
VLFDHVTTDMRLAWEEPFGPVLPIIRVTTVEEAIKISNESEYGLQASIFTTNFPKAFGIAEQLEVGTVHLNNKTQRGTDNFPFLGAKKSG
AGVQGVKYSIEAMTTVKSVVFDIQ

SPy1375
Seq ID 208
MSLKDLGDISYFRLNNEINRPVNGKIPLHKDKEALKAFSAENVLPNTMSFTSITEKIEYLISNDYIESAFIQKYRPEFITELDSIIKSENFRF
KSFMAAYKFYQQYALKTNDGEHYLENLEDRVLFNALYFADGQEDLAKDLAVEMINQRYQPATPSFLNAGRSRRGELVSCFLIQVTDD
MNSIGRSINSALQLSRIGGGVGITLSNLREAGAPIKGYAGAASGVVPVMKLFEDSFSYSNQLGQRQGAGVVYLNVFHPDIIAFLSTKKE
NADEKVRVKTLSLGITVPDKFYELARKNEDMYLFSPYNVEKEYGIPFNYLDITNMYDELVANPKITKTKIKARDLETEISKLQQESGYPYI
INIDTANKANPIDGKIIMSNLCSEILQVQTPSLINDAQEFVEMGTDISCNLGSTNILNMMTSPDFGRSIKTMTRALTFVTDSSSIEAVPTIK

HGNSQAHTFGLGAMGLHSYLAQHHIEYGSPESIEFTDIYFMLLNYWTLVESNNIARERQTTFVGFENSKYANGSYFDKYVTGHFVPKS
DLVKDLFKDHFIPQASDWEALRDAVQKDGLYHQNRLAVAPNGSISYINDCSASIHPITQRIEERQEKKIGKIYYPANGLSTDTIPYYTSA
YDMDMRKVIDVYAAATEHVDQGLSLTLFLRSELPMELYEWKTQSKQTTRDLSILRNYAFNKGIKSIYYIRTFTDDGEEVGANQCESCVI

SPy1389
Seq ID 209
MKELSSAQIRQMWLDFWKSKGHCVEPSANLVPVNDPTLLWINSGVATLKKYFDGSVIPENPRITNAQKSIRTNDIENVGKTARHHTMF
EMLGNFSIGDYFRDEAIEWGFELLTSPDWFDFPKDKLYMTYYPDDKDSYNRWIACGVEPSHLVPIEDNFWEIGAGPSGPDTEIFFDR
GEDFDPENIGLRLLAEDIENDRYIEIWNIVLSQFNADPAVPRSEYKELPNKNIDTGAGLERLAAVMQGAKTNFETDLFMPIIREVEKLSG
KTYDPDGDNMSFKVIADHIRALSFAIGDGALPGNEGRGYVLRRLLRRAVMHGRRLGINETFLYKLVPTVGQIMESYYPEVLEKRDFIEK
IVKREEETFARTIDAGSGHLDSLLAQLKAEGKDTLEGKDIFKLYDTYGFPVELTEELAEDAGYKIDHEGFKSAMKEQQDRARAAVVKG
GSMGMQNETLAGIVEESRFEYDTYSLESSLSVIIADNERTEAVSEGQALLVFAQTPFYAEMGGQVADTGRIKNDKGDTVAEVVDVQK
APNGQPLHTVNVLASLSVGTNYTLEINKERRLAVEKNHTATHLLHAALHNVIGEHATQAGSLNEEEFLRFDFTHFEAVSNEELRHIEQE
VNEQIWNALTITTTETDVETAKEMGAMALFGEKYGKVVRVVQIGNYSVELCGGTHLNNSSEIGLFKIVKEEGIGSGTRRIIAVTGRQAF
EAYRNQEDALKEIAATVKAPQLKDAAAKVQALSDSLRDLQKENAELKEKAAAAAAGDVFKDVQEAKGVRFIASQVDVADAGALRTFA
DNWKQKDYSDVLVLVAAIGEKVNVLVASKTKDVHAGNMIKELAPIVAGRGGGKPDMAMAGGSDASKIAELLAAVAEIV

SPy1390
Seq ID 210
MKNSNKLIASVVTLASVMALAACQSTNDNTKVISMKGDTISVSDFYNETKNTEVSQKAMLNLVISRVFEAQYGDKVSKKEVEKAYHKT
AEQYGASFSAALAQSSLTPETFKRQIRSSKLVEYAVKEAAKKELTTQEYKKAYESYTPTMAVEMITLDNEETAKSVLEELKAEGADFTA
IAKEKTTTPEKKVTYKFDSGATNVPTDVVKAASSLNEGGISDVISVLDPTSYQKKFYIVKVTKKAEKKSDWQEYKKRLKAIIIAEKSKDM
NFQNKVIANALDKANVKIKDKAFANILAQYANLGQKTKAASESSTTSESSKAAEENPSESEQTQTSSAEEPTETEAQTQEPAAQ

SPy1422
Seq ID 211
VLYPTPIAKLIDSYSKLPGIGIKTATRLAFYTIGMSNEDVNDFAKNLLAAKRELTYCSICGNLTDDDPCHICTDTSRDQTTILVVEDAKDV
SAMEKIQEYHGYYHVLHGLISPMNGVGPDDINLKSLITRLMDGKVSEVIVATNATADGEATSMYISRVLKPAGIKVTRLARGLAVGSDIE
YADEVTLLRAIENRTEL

SPy1436
Seq ID 212
MDMSKSNRRTWQGLVVILIAILTTFTTSTVTAARKIRNFPDTTEILLGTKATETPGILPFTGSYQLVLGDLDNLQRPTFAHIQLKDQDEPN
IKRKGLKFNPPGWHNYKLTDANGKTTWLMDRGHLVGYQFSGLNDEPKNLVTMTKYLNTGFSDKNPLGMLYYENRLDSWLALHPNF
WLDYKVTPVYHKNELVPRQVVLQYVGIDENGDLLQIKLGSEKESVDNFGVTSVTLDNVSPLAELDYQTGMMLDSTQNEEDSNLETEE
FEEAA

SPy1494
Seq ID 213
MTSKKACLSSIIVLASLTCGNDTVSANHLSATGDKFDDCSTLVEKDVAPKDELEMLAWSSSQTTDDADRDYEDFLDDDSFISQNETDK
MFENLTDDRLLNELDELDEENEEDEEDTIEPEQNVIMPSDDELFDLTDAVETRLTVSSAPHLEAELPKPHLRSLSDTALRSGEIRGHLD
NKLDALSVTATKLALTMAQKFDLTTHVYSIGESFSEVLAAHYEDRKAESAFSKKKRFHLPIATPDVVIEELRRLVSSIGSSKEDVSVPYS
RKLGMAVAKRKIALPQTGERFSYYPVLLGLMILGLTPIMIPKKINN

SPy1523
Seq ID 214
MAKDKEKQSDDKLVLTEWQKRNIEFLKKKKQQAEEEKKLKEKLLSDKKAQQQAQNASEAVELKTDEKTDSQEIESETTSKPKKTKKV
RQPKEKSATQIAFQKSLPVLLGALLLMAVSIFMITPYSKKKEFSVRGNHQTNLDELIKASKVKASDYWLTLLTSPGQYERPILRTIPWVK
SVHLSYQFPNHFLFNVIEFEIIAYAQVENGFQPILENGKRVDKVRASELPKSFLILNLKDEKAIQQLVKQLTTLPKKLVKNIKSVSLANSKT
TADLLLIEMHDGNVVRVPQSQLTLKLPYYQKLKKNLENDSIVDMEVGIYTTTQEIENQPEVPLTPEQNAADKEGDKPGEHQEQTDNDS
ETPANQSSPQQTPPSPETVLEQAHG

SPy1536
Seq ID 215
MKRLKKIKWWLVGLLALISLLLALFFPLPYYIEMPGGAYDIRTVLQVNGKEDKRKGAYQFVAVGISRASLAQLLYAWLTPFTEISTAEDT
TGGYSDADFLRINQFYMETSQNAAIYQALSLAGKPVTLDYKGVYVLDVNNESTFKGTLHLADTVTGVNGKQFTSSAELIDYVSHLKLG
DEVTVQFTSDNKPKKGVGRIIKLKNGKNGIGIALTDHTSVNSEDTVIFSTKGVGGPSAGLMFTLDIYDQITKEDLRKGRTIAGTGTIGKD
GEVGDIGGAGLKVVAAAEAGADIFFVPNNPVDKEIKKVNPNAISNYEEAKRAAKRLKTKMKIVPVTTVQEALVYLRK

SPy1564
Seq ID 216
MLEHKIDFMVTLEVKEANANGDPLNGNMPRTDAKGYGVMSDVSIKRKIRNRLQDMGKSIFVQANERIEDDFRSLEKRFSQHFTAKTP
DKEIEEKANALWFDVRAFGQVFTYLKKSIGVRGPVSISMAKSLEPIVISSLQITRSTNGMEAKNNSGRSSDTMGTKHFVDYGVYVLKG
SINAYFAEKTGFSQEDAEAIKEVLVSLFENDASSARPEGSMRVCEVFWFTHSSKLGNVSSARVFDLLEYHQSIEEKSTYDAYQIHLNQ
EKLAKYEAKGLTLEILEGL

SPy1604
Seq ID 217
MATKKVHIISHSHWDREWYMAYEQHHMRLINLIDDLLEVFQTDPDFHSFHLDGQTIILDDYLKVRPEREPEIRQAIASGKLRIGPFYILQ
DDFLTSSESNVRNMLIGKEDCDRWGASVPLGYFPDTFGNMGQTPQLMLKAGLQAAAFGRGIRPTGFNNQVDTSEKYSSQFSEISW
QGPDNSRILGLLFANWYSNGNEIPTTEAEARLFWDKKLADAERFASTKHLLMMNGCDHQPVQLDVTKAIALANQLYPDYEFVHSCFE
DYLADLADDLPENLSTVQGEITSQETDGWYTLANTASARIYLKQANTRVSRQLENITEPLAAMAYEVTSTYPHDQLRYAWKTLMQNH
PHDSICGCSVDSVHREMMTRFEKAYEVGHYLAKEAAKQIADAIDTRDFPMDSQPFVLFNTSGHSKTSVAELSLTWKKYHFGQRFPKE
VYQEAQEYLARLSQSFQIIDTSGQVRPEAEILGTSIAFDYDLPKRSFREPYFAIKVRLRLPITLPAMSWKTLALKLGNETTPSETVSLYD
DSNQCLENGFLKVMIQTDGRLTITDKQSGLIYQDLLRFEDCGDIGNEYISRQPNHDQPFYADQGTIKLNIISNTAQVAELEIQQTFAIPIS
ADKLLQAEMEAVIDITERQARRSQEKAELTLTTLIRMEKNNPRLQFTTRFDNQMTNHRLRVLFPTHLKTDHHLADSIFETVKRPNHPDA

TFWKNPSNPQHQECFVSLFDGENGVTIGNYGLNEYEILPDTNTIAITLLRSVGEMGDWGYFPTPEAQCLGKHSLSYSFESITKQTQFA
SYWRAQEGQVPVITTQTNQHEGTLAAEYSYLTGTNDQVALTAFKRRLADNALITRSYNLSNDKTCDFSLSLPNYNAKVTNLLEKDSKQ
STPSQLGKAEILTLAWKKQ

SPy1607
Seq ID 218
MKITKIEKKKRLYLIELDNDESLYVTEDTIVRFMLSKDKVLDNDQLEDMKHFAQLSYGKNLALYFLSFQQRSNKQVADYLRKHEIEEHIIA
DIITQLQEEQWIDDTKLADTYIRQNQLNGDKGPQVLKQKLLQKGIASHDIDPILSQTDFSQLAQKVSQKLFDKYQEKLPPKALKDKITQA
LLTKGFSYDLAKHSLNHLNFDQDNQEIEDLLDKELDKQYRKLSRKYDGYTLKQKLYQALYRKGYNSDDINCKLRNYL

SPy1615
Seq ID 219
MICLLCQQISQTPISITEIIFLRRISSPICQQCQKSFQKIGKSVCATCCANSDIIACRDCLKWENKGYNVNHRSLYCYNAAMKAYFSQYKF
QGDYLLRKVFAVELADVITKYYKGYIPVPVPVSPGCFRERQFNQVSAILEAANVSYLSLFEKLDNTHQSSRTKKERLLVEKSYRLLKVS
NIPDKILIVDDIYTTGSTIIALRKQLAKVANSDIKSLSIAR

SPy1666
Seq ID 220
MKSFSLTFSFLNLLKYGTIKVMTKEFHHVTVLLHETVDMLDIKPDGIYVDATLGGSGHSAYLLSKLGEEGHLYCFDQDQKAIDNAQVTL
KSYIDKGQVTFIKDNFRHLKARLTALGVDEIDGILYDLGVSSPQLDERERGFSYKQDAPLDMRMDRQSLLTAYEVVNTYPFNDLVKIFF
KYGEDKFSKQIARKIEQARAIKPIETTTELAELIKAAKPAKELKKKGHPAKQIFQAIRIEVNDELGAADESIQDAMELLALDGRISVITFHSL
EDRLTKQLFKEASTVDVPKGLPLIPEDMKPKFELVSRKPILPSHSELTANKRAHSAKLRVAKKIRK

SPy1727
Seq ID 221
VTTTEQELTLTPLRGKSGKAYKGTYPNGECVFIKLNTTPILPALAKEQIAPQLLWAKRMGNGDMMSAQEWLNGRTLTKEDMNSKQIIH
ILLRLHKSKKLVNQLLQLNYKIENPYDLLVDFEQNAPLQIQQNSYLQAIVKELKRSLPEFKSEVATIVHGDIKHSNWVITTSGMIFLVDWD
SVRLTDRMYDVAYLLSHYIPRSRWSEWLSYYGYKNNDKVMQKIIWYGQFSHLTQILKCFDKRDMEHVNQEIYALRKFREIFRKK

SPy1785
Seq ID 222
MILTAPMSNLKGFGPKSAEKFQKLDIYTVEDLLLYYPFRYEDFKSKSVFDLVDGEKAVITGLVVTPANVQYYGFKRNRLSFKLRQGEAV
LNVSFFNQPYLADKIELGQEVAVFGKWDATKSAITGMKVLAQVEDDMQPVYRVAQGISQSTLIKAIKSAFEIDAHLELKENLPATLLEKY
RLMGRSQACLAMHFPKDITEYKQALRRIKFEELFYFQMNLQVLKAENKSETNGLPILYSKRAMETKISSLPFILTNAQKRSLDDILSDMS
SGAHMNRLLQGDVGSGKTVIAGLSMYAAYTAGFQSALMVPTEILAEQHYISLQELFPDLSIAILTSGMKAAVKRTVLAAIANGSVDMIV
GTHALIQDSVQYHKLGLVITDEQHRFGVKQRRIFREKGENPDVLMMTATPIPRTLAITAFGEMDVSIIDELPAGRKPIMTRWVKHEQLG
TVLEWVKGELQKDAQVYVISPLIEESEALDLKNAVALHAELSTYFEGIAKVALVHGRMKNDEKDAIMQDFKDKKSHILVSTTVIEVGVNV
PNATIMIIMDADRFGLSQLHQLRGRVGRGYKQSYAVLVANPKTDSGKKRMTIMTETTDGFVLAESDLKMRGSGEIFGTRQSGIPEFQV
ADIVEDYPILEEARKVSAAIVSDPNWIYEKQWQLVAQNIRKKEVYD

SPy1798
Seq ID 223
MKKISKCAFVAISALVLIQATQTVKSQEPLVQSQLVTTVALTQDNRLLVEEIGPYASQSAGKEYYKHIEKIIVDNDVYEKSLEGERTFDIN
YQGIKINADLIKDGKHELTIVNKKDGDILITFIKKGDKVTFISAQKLGTTDHQDSLKKDVLSDKTVPQNQGTQKVVKSGKNTANLSLITKL
SQEDGAILFPEIDRYSDNKQIKALTQQITKVTVNGTVYKDLISDSVKDTNGWVSNMTGLHLGTKAFKDGENTIVISSKGFEDVTITVTKK
DGQIHFVSAKQKQHVTAEDRQSTKLDVTTLEKAIKEADAIIAKESNKDAVKDLAEKLQVIKDSYKEIKDSKLLADTHRLLKDTIESYQAGE
VSINNLTEGTYTLNFKANKENSEESSMLQGAFDKRAKLVVKADGTMEISMLNTALGQFLIDFSIESKGTYPAAVRKQVGQKDINGSYIR
SEFTMPIDDLDKLHKGAVLVSAMGGQESDLNHYDKYTKLDMTFSKTVTKGWSGYQVETDDKEKGVGTERLEKVLVKLGKDLDGDGK
LSKTELEQIRGELRLDHYELTDISLLKHAKNITELHLDGNQITEIPKELFSQMKQLRFLNLRSNHLTYLDKDTFKSNAQLRELYLSSNFIH
SLEGGLFQSLHHLEQLDLSKNRIGRLCDNPFEGLSRLTSLGFAENSLEEIPEKALEPLTSLNFIDLSQNNLALLPKTIEKLRALSTIVASR
NHITRIDNISFKNLPKLSVLDLSTNEISNLPNGIFKQNNQLTKLDFFNNLLTQVEESVFPDVETLNLDVKFNQIKSVSPKVRALIGQHKLTP
QKHIAKLEASLDGEKIKYHQAFSLLDLYYWEQKTNSAIDKELVSVEEYQQLLQEKGSDTVSLLNDMQVDWSIVIQLQKKASNGQYVTV
DEKLLSNDPKDDLTGEFSLKDPGTYRIRKALITKKFATQKEHIYLTSNDILVAKGPHSHQKDLVENGLRALNQKQLRDGIYYLNASMLKT
DLASESMSNKAINHRVTLVVKKGVSYLEVEFRGIKVGKMLGYLGELSYFVDGYQRDLAGKPVGRTKKAEVVSYFTDVTGLPLADRYG
KNYPKVLRMKLIEQAKKDGLVPLQVFVPIMDAISKGSGLQTVFMRLDWASLTTEKAKVVKETNNPQENSHLTSTDQLKGPQNRQQEK
TPTSPPSAATGIANLTDLLAKKATGQSTQETSKTDDTDKAEKLKQLVRDHQTSIEGKTAKDTKTKKSDKKHRSNQQSNGEESSSRYH
LIAGLSSFMIVALGFIIGRKTLFK

SPy1801
Seq ID 224
MNKNKLLRVAMLLSLLAPTAESMTVLAQDVMLETHKATTNETSDSSSKEENNKNAAPTTSDKTDQGPLDASAETNSNSLVNADDKKR
SDSSQSAIGSSDNKAEAENQVDDKSTDHSKSTDHSKPTDQPKPSPSKVDTAPASSLSKQLPEARTPIQSLSPYVSDLDLSEIDIPSVN
TYAAYVEHWSGKNAYTHHLLSRRYGIKADQIDSYLKSTGIAYDSTRINGEKLLQWEKKSGLDVRAIVAIAMSESSLGTQGIATLLGANM
FGYAAFDLDPTQASKFNDDSAIVKMTQDTIIKNKNSNFALQDLKAAKFSRGQLNFASDGGVYFTDTTGSGKRRAQIMEDLDKWIDDH
GGTPAIPAELKVQSSASFASVPAGYKLSKSYDVLGYQASSYAWGQCTWYVYNRAKELGYQFDPFMGNGGDWKYKVGYALSKTPKV
GYAISFAPGQAGADGTYGHVSIVEDVRKDGSILISESNCIGLGKISYRTFTAQQAEQLTYVIGKSKN

SPy1813
Seq ID 225
MDKHLLVKRTLGCVCAATLMGAALATHHDSLNTVKAEEKTVQVQKGLPSIDSLHYLSENSKKEFKEELSKAGQESQKVKEILAKAQQA
DKQAQELAKMKIPEKIPMKPLHGSLYGGYFRTWHDKTSDPTEKDKVNSMGELPKEVDLAFIFHDWTKDYSLFWKELATKHVPKLNKQ
GTRVIRTIPWRFLAGGDNSGIAEDTSKYPNTPEGNKALAKAIVDEYVYKYNLDGLDVDVEHDSIPKVDKKEDTAGVERSIQVFEEIGKLI
GPKGVDKSRLFIMDSTYMADKNPLIERGAPYINLLLVQVYGSQGEKGGWEPVSNRPEKTMEERWQGYSKYIRPEQYMIGFSFYEEN
AQEGNLWYDINSRKDEDKANGINTDITGTRAERYARWQPKTGGVKGGIFSYAIDRDGVAHQPKKYAKQKEFKDATDNIFHSDYSVSK
ALKTVMLKDKSYDLIDEKDFPDKALREAVMAQVGTRKGDLERFNGTLRLDNPAIQSLEGLNKFKKLAQLDLIGLSRITKLDRSVLPANM
KPGKDTLETVLETYKKDNKEEPATIPPVSLKVSGLTGLKELDLSGFDRETLAGLDAATLTSLEKVDISGNKLDLAPGTENRQIFDTMLST

ISNHVGSNEQTVKFDKQKPTGHYPDTYGKTSLRLPVANEKVDLQSQLLFGTVTNQGTLINSEADYKAYQNHKIAGRSFVDSNYHYNN
FKVSYENYTVKVTDSTLGTTTDKTLATDKEETYKVDFFSPADKTKAVHTAKVIVGDEKTMMVNLAEGATVIGGSADPVNARKVFDGQL
GSETDNISLGWDSKQSIIFKLKEDGLIKHWRFFNDSARNPETTNKPIQEASLQIFNIKDYNLDNLLENPNKFDDEKYWITVDTYSAQGE
RATAFSNTLNNITSKYWRVVFDTKGDRYSSPVVPELQILGYPLPNADTIMKTVTTAKELSQQKDKFSQKMLDELKIKEMALETSLNSKI
FDVTAINANAGVLKDCIEKRQLLKK

SPy1821
Seq ID 226
MIEASKLKAGMTFEAEGKLIRVLEASHHKPGKGNTIMRMKLRDVRTGSTFDTTYRPDEKFEQAIIETVPAQYLYKMDDTAYFMNTDTY
DQYEIPVANVEQELLYILENSDVKIQFYGSEVIGVTVPTTVELTVAETQPSIKGATVTGSGKPATLETGLVVNVPDFIEAGQKLIINTAEG
TYVSRA

SPy1916
Seq ID 227
MTKTLPKDFIFGGATAAYQAEGATHTDGKGPVAWDKYLEDNYWYTAEPASDFYNRYPVDLKLSEEFGVNGIRISIAWSRIFPTGKGEV
NPKGVEYYHNLFAECHKRHVEPFVTLHHFDTPEALHSDGDFLNRENIEHFVNYAEFCFKEFSEVNYWTTFNEIGPIGDGQYLVGKFPP
GIQYDLAKVFQSHHNMMVSHARAVKLFKDSGYSGEIGVVHALPTKYPFDANNPDDVRAAELEDIIHNKFILDATYLGKYSDKTMEGVN
HILEVNGGELDLREEDFAALDAAKDLNDFLGINYYMSDWMQAFDGETEIIHNGKGEKGSSKYQIKGVGRRKAPVDVPKTDWDWIIFP
QGLYDQIMRVKADYPNYKKIYITENGLGYKDEFVDNTVYDGGRIDYVKKHLEVISDAISDGANVKGYFMWSLMDVFSWSNGYEKRYG
LFYVDFETQERYPKKSAYWYKKVAETQVIE

SPy1972
Seq ID 228
MKKKVNQGSKRYQYLLKKWGIGFVIAATGTVVLGCTPSILTHQVAAKTIVGLARDEAQQGDGNAKSGDGLQSSSKEAKPVLDSSSAN
PASIAEHHLRMHFKTLPAGESLGSLGLWVWGDVDQPSKDWPNGAITMTKAKKDDYGYYLDVPLAAKHRQQVSYLINNKAGENLSKD
QHISLLTPKMNEVWIDENYHAHAYRPLKKGYLRINYHNQSGHYDNLAVWTFKDVKTPTTDWPNGLDLSHKGHYGAYVDVPLKEGAN
EIGFLILDKSKTGDAIKVQPKDYLFKELDNHTQVFVKDTDPKVYNNPYYIDQVSLKGAEQTTPNEIKAIFTTLDGLDEDAVKQNIKITDKA
GKTVAIDELTLDRDKSVMTLKGDFKAQGAVYTVTFGEVSQVARQSWQLKDKLYAYDGELGATLAKDGSVDLALWSPSADTVKVVVY
DKQDQTRVVGQADLTKSDKGVWRAHLTSDSVKGISDYTGYYYLYEITRGQEKVMVLDPYAKSLAAWNDATATDDIKTAKAAFIDPSK
LGPTGLDFAKINNFKKREDAIIYEAHVRDFTSDKALEGKLTHPFGTFSAFVEQLDYLKDLGVTHVQLLPVLSYFYANELDKSRSTAYTS
SDNNYNWGYDPQHYFALSGMYSANPNDPALRIAELKNLVNEIHKRGMGVIFDVVYNHTARTYLFEDLEPNYYHFMNADGTARESFG
GGRLGTTHAMSRRILVDSITYLTREFKVDGFRFDMMGDHDAAAIEQAFKAAKAINPNTIMIGEGWRTYQGDEGKKEIAADQDWMKAT
NTVGVFSDDIRNTLKSGFPNEGTAAFITGGAKNLEGLFKTIKAQPGNFEADAPGDVVQYIAAHDNLTLHDVIAKSINKDPKVAEEEIHKR
IRLGNTMILTAQGTAFIHSGQEYGRTKQLLNPDYKTKASDDKVPNKATLIDAVAQYPYFIHDSYDSSDAVNHFDWAKATDSIAHPISNQ
TKAYTQGLIALRRSTDAFTKATKAEVDRDVTLITQAGQDGIQQEDLIMGYQTVASNGDRYAVFVNADNKTRKVVLPQAYRYLLGAQVL
VDAEQAGVTAIAKPKGVQFTKEGLTIEGLTALVLKVSSKTANPSQQKSQTDNHQTKTPDGSKDLDKSLMTRPKRAKTNQKLPKTGEA
SSKGLLAAGIALLLLAISLLMKRQKD

SPy1979
Seq ID 229
MKNYLSIGVIALLFALTFGTVKSVQAIAGYGWLPDRPPINNSQLVVSMAGIVEGTDKKVFINFFEIDLTSQPAHGGKTEQGLSPKSKPFA
TDNGAMPHKLEKADLLKAIQKQLIANVHSNDGYFEVIDFASDATITDRNGKVYFADKDGSVTLPTQPVQEFLLKGHVRVRPYKEKPVQ
NQAKSVDVEYTVQFTPLNPDDDFRPGLKDTKLLKTLAIGDTITSQELLAQAQSILNKTHPGYTIYERDSSIVTHDNDIFRTILPMDQEFTY
HVKNREQAYEINPKTGIKEKTNNTDLVSEKYYVLKQGEKPYDPFDRSHLKLFTIKYVDVNTNELLKSEQLLTASERNLDFRDLYDPRDK
AKLLYNNLDAFDIMDYTLTGKVEDNHDKNNRVVTVYMGKRPKGAKGSYHLAYDKDLYTEEERKAYSYLRDTGTPIPDNPKDK

SPy1983
Seq ID 230
MLTSKHHNLNKLVWRYGLTSAAAVLLAFGGGASSVKAEVSSTTMTSSQRESKIKEIEESLKKYPEVSNEKFWERKWYGTYFKEEDFQ
KELKDFTEKRLKEILDLIGKSGIKGDRGETGPAGPAGPQGKTGERGAQGPKGDRGEQGIQGKAGEKGERGEKGDKGETGERGEKG
EAGIQGPQGEAGKDGAPGKDGAPGEKGEKGDRGETGAQGPVGPQGEKGETGAQGPAGPQGEAGKPGEQGPAGPQGEAGQPGE
KAPEKSPEGEAGQPGEKAPEKSKEVTPAAEKPADKEANQTPERRNGNMAKTPVANNHRRLPATGEQANPFFTAAAVAVMTTAGVL
AVTKRKENN

SPy1991
Seq ID 231
MILLIDNYDSFTYNLAQYLSEFDETIVLYNQDPNLYDMAKKANALVLSPGPGWPKEANQMPKLIQDFYQTKPILGVCLGHQAIAETLGG
TLRLAKRVMHGRQSTIETQGPASLFRSLPQEITVMRYHSIVVDQLPKGFSVTARDCDDQEIMAFEHHTLPLFGLQFHPESIGTPDGMT
MIANFIAAIPR

SPy2000
Seq ID 232
VSKYLKYFSIITLFLTGLILVACQQQKPQTKERQRKQRPKDELVVSMGAKLPHEFDPKDRYGVHNEGNITHSTLLKRSPELDIKGELAK
TYHLSEDGLTWSFDLHDDFKFSNGEPVTADDVKFTYDMLKADGKAWDLTFIKNVEVVGKNQVNIHLTEAHSTFTAQLTEIPIVPKKHY
NDKYKSNPIGSGPYMVKEYKAGEQAIFVRNPYWHGKKPYFKKWTWVLLDENTALAALESGDVDMIYATPELADKKVKGTRLLDIPSN
DVRGLSLPYVKKGVITDSPDGYPVGNDVTSDPAIRKALTIGLNRQKVLDTVLNGYGKPAYSIIDKTPFWNPKTAIKDNKVAKAKQLLTK
AGWKEQADGSRKKGDLDAAFDLYYPTNDQLRANLAVEVAEQAKALGITIKLKASNWDEMATKSHDSALLYAGGRHHAQQFYESHHP
SLAGKGWTNITFYNNPTVTKYLDKAMTSSDLDKANEYWKLAQWDGKTGASTLGDLPNVWLVSLNHTYIGDKRINVGKQGVHSHGHD
WSLLTNIAEWTWDESTK

SPy2006
Seq ID 233
VKKTYGYIGSVAAILLATHIGSYQLGKHHMGSATKDNQIAYIDDSKGKAKAPKTNKTMDQISAEEGISAEQIVVKITDQGYVTSHGDHYH
FYNGKVPYDAIISEELLMTDPNYRFKQSDVINEILDGYVIKVNGNYYVYLKPGSKRKNIRTKQQIAEQVAKGTKEAKEKGLAQVAHLSK
EEVAAVNEAKRQGRYTTDDGYIFSPTDIIDDLGDAYLVPHGNHYHYIPKKDLSPSELAAAQAYWSQKQGRGARPSDYRPTPAPAPGR
RKAPIPDVTPNPGQGHQPDNGGYHPAPPRPNDASQNKHQRDEFKGKTFKELLDQLHRLDLKYRHVEEDGLIFEPTQVIKSNAFGYVV

PHGDHYHIIPRSQLSPLEMELADRYLAGQTEDDDSGSDHSKPSDKEVTHTFLGHRIKAYGKGLDGKPYDTSDAYVFSKESIHSVDKS
GVTAKHGDHFHYIGFGELEQYELDEVANWVKAKGQADELAAALDQEQGKEKPLFDTKKVSRKVTKDGKVGYMMPKDGKDYFYARD
QLDLTQIAFAEQELMLKDKKHYRYDIVDTGIEPRLAVDVSSLPMHAGNATYDTGSSFVIPHIDHIHVVPYSWLTRDQIATIKYVMQHPEV
RPDIWSKPGHEESGSVIPNVTPLDKRAGMPNWQIIHSAEEVQKALAEGRFATPDGYIFDPRDVLAKETFVWKDGSFSIPRADGSSLRT
INKSDLSQAEWQQAQELLAKKNAGDATDTDKPKEKQQADKSNENQQPSEASKEEEKESDDFIDSLPDYGLDRATLEDHINQLAQKA
NIDPKYLIFQPEGVQFYNKNGELVTYDIKTLQQINP

SPy2009
Seq ID 234
MRRAENNKHSRYSIRKLSVGVTSIAIASLFLGKVAYAVDGIPPISLTQKTTATTSENWHHIDKDGLIPLGISLEAAKEEFKKEVEESRLSE
AQKETYKQKIKTAPDKDKLLFTYHSEYMTAVKDLPASTESTTQPVEAPVQETQASASDSMVTGDSTSVTTDSPEETPSSESPVAPALS
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SPy2010
Seq ID 235
LRKKQKLPFDKLAIALMSTSILLNAQSDIKANTVTEDTPATEQAVETPQPTAVSEEAPSSKETKTPQTPDDAEETIADDANDLAPQAPA
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ETQYPDMTPSERLDLAKKVLMSSATALYDEDEKAYFSPRQQGAGAVDAKKASAATMYVTDKDNTSSKVHLNNVSDKFEVTVTVHNK
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PYIGFRGDFGNLSALEKPIYDSKDGSSYYHEANSDAKDQLDGDGLQFYALKNNFTALTTESNPWTIIKAVKEGVENIEDIESSEITETIFA
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KDQLPTTNDKDTNRLHLLKLVMTTFFLGLVAHIFKTKRTED

SPy2016
Seq ID 236
MNIRNKIENSKTLLFTSLVAVALLGATQPVSAETYTSRNFDWSGDDWSGDDWPEDDWSGDGLSKYDRSGVGLSQYGWSKYGWSS
DKEEWPEDWPEDDWSSDKKDETEDKTRPPYGEALGTGYEKRDDWGGPGTVATDPYTPPYGGALGTGYEKRDDWGGPGTVATDP
YTPPYGGALGTGYEKRDDWRGPGHIPKPENEQSPNPLHIPEPPQIEWPQWNGFDGLSFGPSDWGQSEDTPPSEPRVPEKPQHTP
QKNPQESDFDRGFSAGLKAKNSGRGIDFEGFQYGGWSDEYKKGYMQAFGTPYTPSAT

SPy2018
Seq ID 237
MAKNNTNRHYSLRKLKTGTASVAVALTVLGAGFANQTEVKANGDGNPREVIEDLAANNPAIQNIRLRYENKDLKARLENAMEVAGRD
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NLTAELDKVKEDKQISDASRQGLRRDLDASREAKKQVEKDLANLTAELDKVKEEKQISDASRQGLRRDLDASREAKKQVEKALEEAN
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SPy2025
Seq ID 238
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SPy2039
Seq ID 239
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EQSFVGQHAATGCVATATAQIMKYHNYPNKGLKDYTYTLSSNNPYFNHPKNLFAAISTRQYNWNNILPTYSGRESNVQKMAISELMA
DVGISVDMDYGPSSGSAGSSRVQRALKENFGYNQSVHQINRGDFSKQDWEAQIDKELSQNQPVYYQGVGKVGGHAFVIDGADGRN
FYHVNWGWGGVSDGFFRLDALNPSALGTGGGAGGFNGYQSAVVGIKP

SPy2043
Seq ID 240
MNLLGSRRVFSKKCRLVKFSMVALVSATMAVTTVTLENTALARQTQVSNDVVLNDGASKYLNEALAWTFNDSPNYYKTLGTSQITPA
LFPKAGDILYSKLDELGRTRTARGTLTYANVEGSYGVRQSFGKNQNPAGWTGNPNHVKYKIEWLNGLSYVGDFWNRSHLIADSLGG
DALRVNAVTGTRTQNVGGRDQKGGMRYTEQRAQEWLEANRDGYLYYEAAPIYNADELIPRAVVVSMQSSDNTINEKVLVYNTANGY
TINYHNGTPTQK

SPy2059
Seq ID 241
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SPy2110
Seq ID 242
MVSLEEDKVTVQPDIKVIKRDGRLVNFDSTKIYSALLKASMKVTRMSPLVEAKLEAISDRIIAEIIERFPTNIKIYEIQNIVEHKLLAANEYAI AKEYINYRTQRDFARSQATDINFSIDKLINKDQTVVNENANKDSDVFNTQRDLTAGIVGKSIGLKMLPSHVANAHQKGDIHYHDLDYSP YTPMTNCCLIDFKGMLANGFKIGNAEVESPKSIQTATAQISQIIANVASSQYGGCTADRIDEFLAPYAELNFKKHMADAKKWIVETKRE SYAFEKTQKDIYDAMQSLEYEINTLFTSNGQTPFTSLGFGLGTSWFEREIQKAILTIRINGLGSEHRTAIFPKLIFTVKRGLNLEPDSPNY DIKTLALECATKRMYPDMLSYDKIIDLTGSFKSPMGCRSFLQGWKDENGQDVTSGRMNLGVVTLNLPRIAMESNGDMDKFWELFNE RMLISKDALIYRVERVTEAKPANAPILYQYGAFGKRLEKTGNVNDLFKNRRATVSLGYIGLYEVASVFYGGQWEGNPDAKAFTLSIVKA MKQACEDWSDEYGYHFSVYSTPSESLTDRFCRLDTEKFGIVTDITDKEYYTNSFHYDVRKSPTPFEKLDFEKDYPEAGASGGFIHYC EYPVLQQNPKALEAVWDYAYDRVGYLGTNTPIDKCYNCQFEGDFTPTERGFTCPNCGNNDPKTVDVVKRTCGYLGNPQARPMVNG RHKEISARVKHMNGSTIKYPGL

SPy2127
Seq ID 243
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SPy2191
Seq ID 244
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SPy2211
Seq ID 245
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ARF0450
Seq ID 246
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ARF0569
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ARF0694
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ARF0700
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ARF1007
Seq ID 250
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ARF1145
Seq ID 251
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ARF1208
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ARF1262
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ARF1294
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ARF1316
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ARF1352
Seq ID 256
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ARF1481
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ARF1557
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ARF1629
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ARF1654
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ARF2027
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ARF2093
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ARF2207
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CRF0038
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CRF0122
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CRF0406
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CRF0416
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CRF0507
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CRF0628
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CRF0727
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CRF0742
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CRF0784
Seq ID 274
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CRF0854
Seq ID 275
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CRF0875
Seq ID 276
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CRF0907
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CRF0979
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CRF1068
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CRF1203
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CRF1225
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CRF1236
Seq ID 283
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CRF1362
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CRF1524
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CRF1525
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CRF1749
Seq ID 290
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CRF1903.

Seq ID 291
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CRF1964
Seq ID 292
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CRF2055
Seq ID 293
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CRF2091
Seq ID 294
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CRF2096
Seq ID 295
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CRF2104
Seq ID 296
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CRF2116
Seq ID 297
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CRF2153
Seq ID 298
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NRF0001
Seq ID 299
itlltkqtqqlfrkpslsnnllkhllvkrmslsmflkqkhqltkpkasmlrpqnnkttisfhhggdqtikihgptlts

NRF0003
Seq ID 300
sgrqdsnlrhlgpkpstlps

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(54) Title: STREPTOCOCCUS PYOGENES ANTIGENS

(57) Abstract: The present invention discloses isolated nucleic acid molecules encoding a hyperimmune serum reactive antigen or a fragment thereof as well as hyperimmune serum reactive antigens or fragments thereof from S. pyogenes, methods for isolating such antigens and specific uses therefor

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C07K14/315 C12R1/46 C07K16/12 C12Q1/68
A61K39/09 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, Sequence Search, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/34771 A (MARGARIT Y ROS IMMACULADA ; CHIRON SPA (IT); GRANDI GUIDO (IT); MASIGN) 2 May 2002 (2002-05-02) page 3679; claims; example 1662; sequence 5153	1,2, 5-11, 14-37
X	DATABASE EMBL Streptococcus pyogenes 1 June 2001 (2001-06-01), FERRETTI J.J., ET AL.: "Hypothetical protein SPy0012" XP002293513 retrieved from EBI Database accession no. Q9A202 abstract	1,2, 5-11, 14-37

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 August 2004	06. 12. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Madruga, J

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	-& DATABASE EMBL 16 April 2001 (2001-04-16), FERRETTI J.J., ET AL.: "Streptococcus pyogenes M1 GAS, section 1 of 167 of the complete genome" XP002293514 retrieved from EBI Database accession no. AE006472 abstract	1,2, 5-11, 14-37
X	-& FERRETTI J J ET AL: "Complete genome sequence of an M1 strain of Streptococcus pyogenes" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 98, no. 8, 10 April 2001 (2001-04-10), pages 4658-4663, XP002168716 ISSN: 0027-8424 the whole document -----	1,2, 5-11, 14-37
X	DATABASE EMBL Streptococcus pyogenes (serotype M18) 1 October 2002 (2002-10-01), SMOOT J.C., ET AL.: "Hypothetical protein spyM18_0011" XP002293515 retrieved from EBI Database accession no. Q8P323 abstract	1,2, 5-11, 14-37
X	-& DATABASE EMBL 28 March 2002 (2002-03-28), SMOOT J.C., ET AL.: "Streptococcus pyogenes strain MGAS8232, section 1 of 173 of the complete genome." XP002293516 retrieved from EBI Database accession no. AE009953 abstract	1,2, 5-11, 14-37
X	-& SMOOT J C ET AL: "Genome sequence and comparative microarray analysis of serotype M18 group A Streptococcus strains associated with acute rheumatic fever outbreaks" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE. WASHINGTON, US, vol. 99, no. 7, 2 April 2002 (2002-04-02), pages 4668-4673, XP002267116 ISSN: 0027-8424 the whole document ----- -/--	1,2, 5-11, 14-37

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL Streptococcus pyogenes (serotype M3) 1 October 2002 (2002-10-01), BERES S.B., ET AL: "Hypothetical protein SpyM3_0009" XP002293517 retrieved from EBI Database accession no. Q8K8Z4 abstract	1,2, 5-11, 14-37
X	-& BERES STEPHEN B ET AL: "Genome sequence of a serotype M3 strain of group A Streptococcus: Phage-encoded toxins, the high-virulence phenotype, and clone emergence" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 99, no. 15, 23 July 2002 (2002-07-23), pages 10078-10083, XP002293512 ISSN: 0027-8424 -----	1,2, 5-11, 14-37
A	WO 02/059148 A (CISTEM BIOTECHNOLOGIES GMBH ; AHSEN UWE (AT); ETZ HILDEGARD (AT); HAFN) 1 August 2002 (2002-08-01) cited in the application page 49 - page 53; claim 10 -----	
P,A	HENICS T ET AL: "Small-fragment genomic libraries for the display of putative epitopes from clinically significant pathogens." BIOTECHNIQUES, vol. 35, no. 1, July 2003 (2003-07), pages 196-209, XP002293668 ISSN: 0736-6205 the whole document -----	
A	REID SEAN D ET AL: "Postgenomic analysis of four novel antigens of group A Streptococcus: Growth phase-dependent gene transcription and human serologic response" JOURNAL OF BACTERIOLOGY, vol. 184, no. 22, November 2002 (2002-11), pages 6316-6324, XP002293669 ISSN: 0021-9193 the whole document -----	

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REID SEAN D ET AL: "Multilocus analysis of extracellular putative virulence proteins made by group A Streptococcus: Population genetics, human serologic response, and gene transcription" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 98, no. 13, 19 June 2001 (2001-06-19), pages 7552-7557, XP002293670 ISSN: 0027-8424 the whole document -----	
A	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2002, VANDERMEID K R ET AL: "Utilization of human antibodies to open reading frame proteins for evaluating opsonophagocytic activity against Streptococcus pyogenes" XP002293671 Database accession no. PREV200200585381 abstract & ABSTRACTS OF THE GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 102, 2002, page 160, 102ND GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY; SALT LAKE CITY, UT, USA; MAY 19-23, 2002 ISSN: 1060-2011 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/002087

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 5-11, 14-37 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention: 1; claims 1,2,5-11,14-37(all in part, as applicable)

A nucleic acid encoding a hyperimmune serum reactive antigen, a hyperimmune serum reactive antigen, a fragment of said hyperimmune serum reactive antigen; an antibody against said hyperimmune serum reactive antigen or fragment; a process for producing said nucleic acid, hyperimmune serum reactive antigen, fragment or antibody; a pharmaceutical composition comprising said nucleic acid, hyperimmune serum reactive antigen, fragment or antibody; methods of identifying an agonist or antagonist; methods of diagnosis, uses of the nucleic acid, the hyperimmune serum reactive antigen or fragment in the manufacture of an aptamer, spiegelmer, ribozyme, antisense oligonucleotide or siRNA, all of them relating to the nucleic acid of SEQ ID NO: 1, the hyperimmune serum reactive antigen of SEQ ID NO: 151 and the fragment comprising amino acids 4-44 of SEQ ID NO: 151.

Inventions: 2-150; claims: 1-37 (all in part and as applicable)

A nucleic acid encoding a hyperimmune serum reactive antigen, a hyperimmune serum reactive antigen, a fragment of said hyperimmune serum reactive antigen; an antibody against said hyperimmune serum reactive antigen or fragment; a process for producing said nucleic acid, hyperimmune serum reactive antigen, fragment or antibody; a pharmaceutical composition comprising said nucleic acid, hyperimmune serum reactive antigen, fragment or antibody; methods of identifying an agonist or antagonist; methods of diagnosis, uses of the nucleic acid, the hyperimmune serum reactive antigen or fragment in the manufacture of a medicament, an aptamer, spiegelmer, ribozyme, antisense oligonucleotide or siRNA, all of them relating to the nucleic acid of SEQ ID NOs: 2-150 and the polypeptides encoded by said nucleic acid, SEQ ID NO: 152-300, respectively

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Inventions: 151-172; claims 1,2,5-11,14-37(all in part, as applicable).

As for invention 1, all relating to a fragment of SEQ ID NO: 151, comprising amino acids:
57-65 (Invention 151), 67-98 (Inv. 152), 101-107, 109-125, 131-144, 146-159, 168-173, 181-186 , 191-200, 206-213, 229-245, 261-269, 288-301 , 304-317, 323-328, 350-361, 374-384, 388-407 , 416-425, 1-114, 18-33 (Inv. 171) and 62-72 (Inv. 172) of SEQ ID NO: 151, respectively.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002087

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0234771	A	02-05-2002	AU	1412702	A	06-05-2002
			CA	2425303	A1	02-05-2002
			EP	1328543	A2	23-07-2003
			WO	0234771	A2	02-05-2002
WO 02059148	A	01-08-2002	AT	410798	B	25-07-2003
			AT	1302001	A	15-12-2002
			BR	0207067	A	15-06-2004
			CA	2436057	A1	01-08-2002
			CZ	20032201	A3	17-03-2004
			WO	02059148	A2	01-08-2002
			EP	1355930	A2	29-10-2003
			JP	2004531476	T	14-10-2004
			NO	20033364	A	24-09-2003